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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	056291-5004-02
First Inventor	John R. Evans
Title	FORMULATION
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☐ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☑ **Specification** [*Total Pages* 23]
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☑ **Drawing(s)** (*35 U.S.C. 113*) [*Total Sheets* 1]
5. **Oath or Declaration** [*Total Sheets* 1]
   a. ☐ Newly executed (original or copy)
   b. ☑ A copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) name in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☐ **Application Data Sheet.** See 37 CFR 1.76
7. ☐ **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a. – c. are required)
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ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet & document(s))
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10. ☐ **37 CFR 3.73(b) Statement** *(when there is an assignee)* ☐ **Power of Attorney**
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
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    (if foreign priority is claimed)
16. ☐ **Nonpublication Request** under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☐ Other:_____

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☑ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 10/872,784

Prior application information: *Examiner* San Ming R. Hui *Art Unit:* 1617

19. CORRESPONDENCE ADDRESS

☑ The address associated with Customer Number: 09629 ***OR*** ☐ Correspondence address below

Name					
Address					
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FORMULATION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available

antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a

pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20
Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically

significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of

formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1} .

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain

some water and possibly other organic solvents, for example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.

17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and difficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still achieved by the formulation of the invention.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v							
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols

	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site

	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+

0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

A further feature of the invention is a method of treating a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

Preferably 5ml of the intramuscular injection is administered.

A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably treating breast cancer.

Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary

pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol

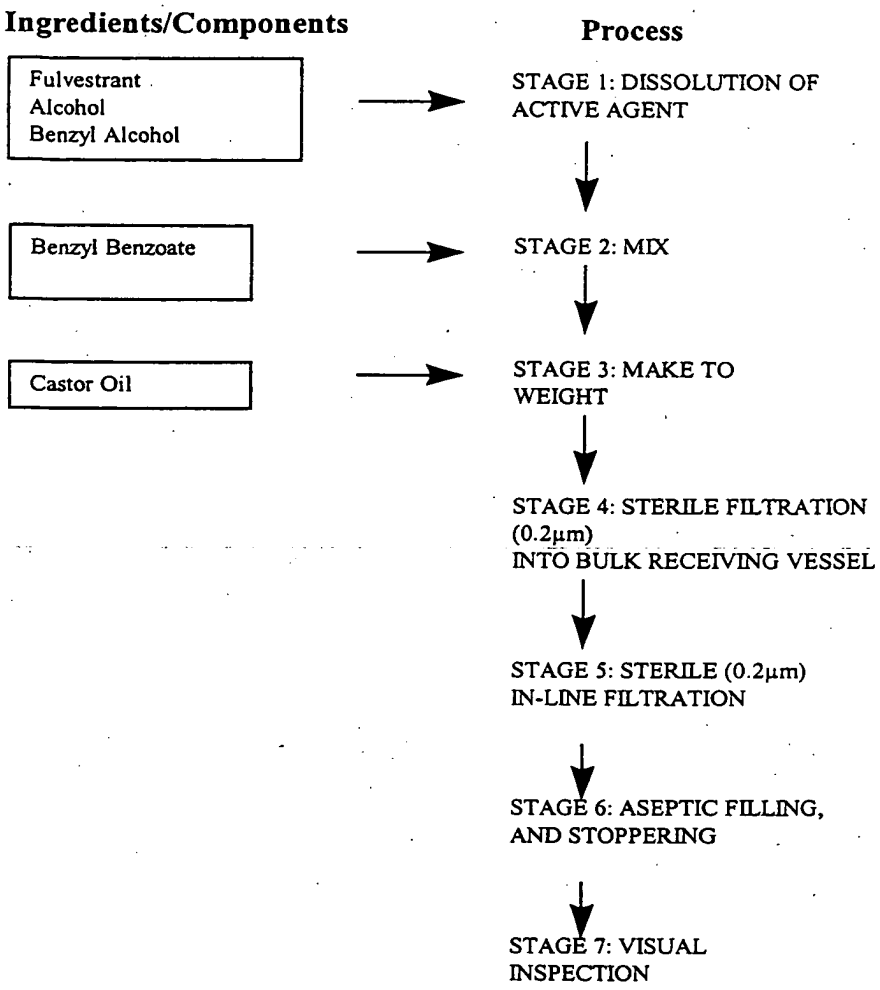
10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ for at least 2 weeks.

2. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks.

3. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks.

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7. A pharmaceutical formulation as claimed in any claim from 1 to 6 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

8. A pharmaceutical formulation as claimed in claim 7 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

9. A pharmaceutical formulation as claimed in claim 7 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 7 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

11. A pharmaceutical formulation as claimed in claim 7 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 7 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 7 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

15. A pharmaceutical formulation as claimed in any claim from 1 to 14 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

16. A pharmaceutical formulation as claimed in any claim from 1 to 15 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

17. A pharmaceutical formulation as claimed in any claim from 1 to 16 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1} .

18. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

19. A pharmaceutical formulation as claimed in claim 18 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

20. A pharmaceutical formulation as claimed in any of claims 1-19 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

21. A method of treating a benign or malignant diseases of the breast or reproductive tract by administration to a human in need of such treatment by intramuscular a pharmaceutical formulation as claimed in claims 1 to 19.

22. A method as claimed in claim 21 for treating breast cancer.

23. A syringe or vial containing a pharmaceutical formulation as defined in claim 20.

ABSTRACT

TITLE: Formulation

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

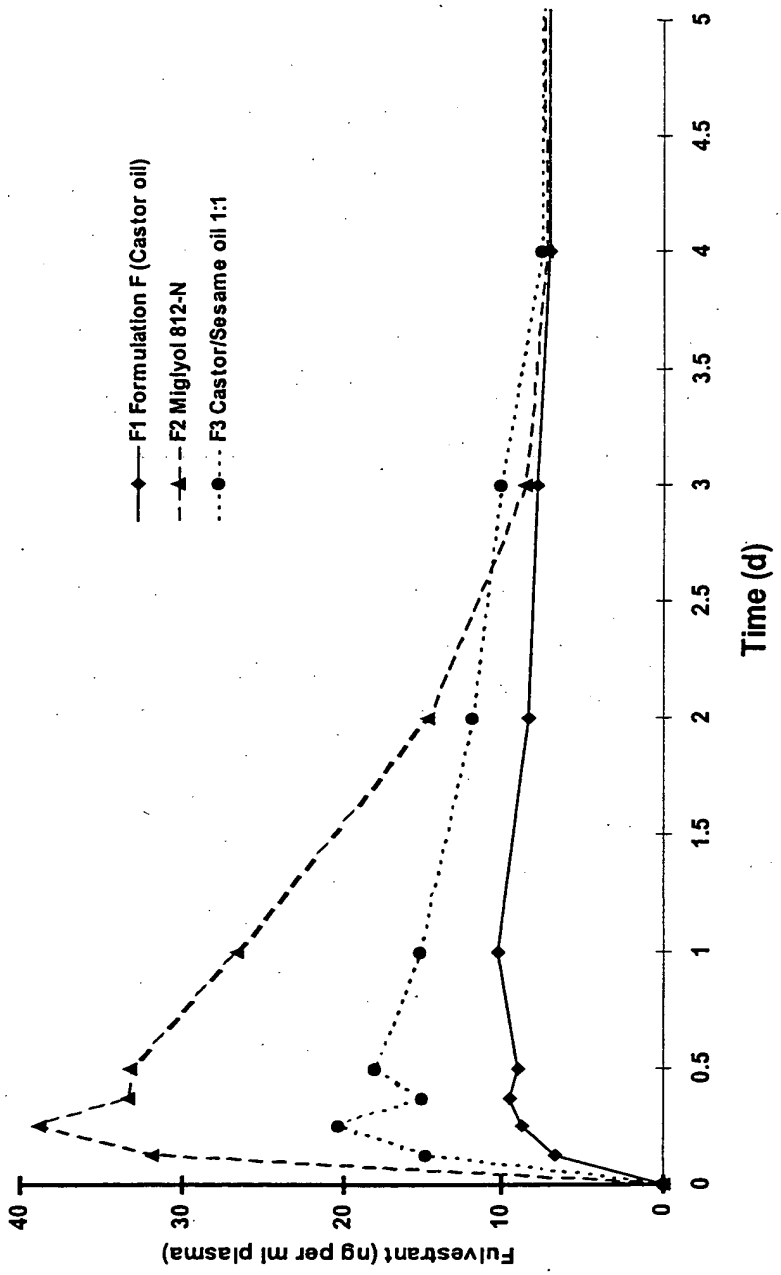

Figure 1

Z70635

Z70635/US

FOR UTILITY/DESIGN CIP/PCT NATIONAL/PLANT ORIGINAL/SUBSTITUTE/SUPPLEMENTAL DECLARATIONS

RULE 63 (37 C.F.R. 63) DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PM & S FORM

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED

FORMULATION

the specification of which (CHECK applicable BOX(ES))

X A. ☐ is attached hereto.

BOX(ES) → B. ☐ was filed on _____ as U.S. Application No. _____

→ → C. ☐ was filed as PCT International Application No. PCT/ _____ on _____

and (if applicable to U.S. or PCT application) was amended on _____

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first Laid-open or Published	Date Patented or Granted	Priority NOT Claimed
0000313.7	GB	10 January 2000			
0008837.7	GB	12 April 2000			

If more prior foreign applications, X box *at bottom* and continue on attached page.

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C. 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT International filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status pending, abandoned, patented	Priority NOT Claimed

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Madison & Sutro LLP, Intellectual Property Group, 1100 New York Avenue, N.W., Ninth Floor, East Tower, Washington, D.C. 20005-3918, telephone number (202) 861-3000 (to whom all communications are to be directed), and the below-named persons (of the same address) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete names/numbers below of persons no longer with their firm and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or a below attorney in writing to the contrary.

Paul N. Kokulis	16773	Dale S. Lazar	28872	Mark G. Paulson	30793	Michael R. Dzwonczyk	36787
Raymond F. Lippitt	17519	Paul E. White, Jr.	32011	Stephen C. Glazier	31361	W. Patrick Bengtsson	32456
G. Lloyd Knight	17698	Glenn J. Perry	28458	Paul F. McQuade	31542	Jack S. Barufka	37087
Carl G. Love	18781	Kendrew H. Colton	30368	Ruth N. Morduch	31044	Adam R. Hess	41835
Kevin E. Joyce	20508	G. Paul Edgell	24238	Richard H. Zaitlen	27248		
George M. Sirilla	18221	Lynn E. Eccleston	35861	Roger R. Wise	31204		
Donald J. Bird	25323	Timothy J. Klima	34852	Jay M. Finkelstein	21082		
Peter W. Gowdey	25872	David A. Jakopin	32995	Anita M. Kirkpatrick	32617		

(1) INVENTOR'S SIGNATURE: John R Evans Date: 25th January 2001

First	Middle Initial	Family Name
John	R	EVANS

Residence City	State/Foreign Country	Country of Citizenship
Macclesfield, Cheshire	United Kingdom	British

Post Office Address	(include Zip Code)
Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom	SK10 4TG

(2) INVENTOR'S SIGNATURE: Rosalind U Grundy Date: 25th January 2001

First	Middle Initial	Family Name
ROSALIND	U	GRUNDY

Residence City	State/Foreign Country	Country of Citizenship
Macclesfield, Cheshire	United Kingdom	British

Post Office Address	(include Zip Code)
Charter Way, Macclesfield, Cheshire, SK10 2NA, United Kingdom	SK10 2NA

FOR ADDITIONAL INVENTORS, "X" box ☐ and proceed on the attached page to list each additional inventor.

☐ See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. PM (M#)

PAT-116 11/99

PATENT
Attorney Docket **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re **Continuation** Application of:	)	Group Art Unit: **Not Assigned**
John R. Evans *et. al*	)	Examiner: **Not Assigned**
Continuation of Application No. **10/872,784**	)	
Application No. **Not Assigned**	)	
Filed: **October 15, 2008**	)	
For: FORUMLATION	)	Date: October 15, 2008

PRELIMINARY AMENDMENT

Prior to examination on the merits, please amend the above-referenced application as follows:

Amendments to the Specification begin on page 2 of this paper.

Remarks begin on page 3 of this paper.

Amendments to the Specification:

On page 1, please after the title, please insert the following paragraph:

This application is a Continuation Application of copending U.S. Patent Application No. 10/872,784, filed June 22, 2004, which claims benefit of U.S. Patent Application No. 09/756,291, filed January 9, 2001 which claims the benefit of Great Britain Application No. 0008837.7 filed April 12, 2000 and Great Britain Application No. 0000313.7, filed January 10, 2000, all of which are incorporated herein by reference in their entireties.

REMARKS

The specification has been amended to update the priority data. Applicants submit that the amendments to the specification do not introduce prohibited new matter.

Respectfully submitted
Morgan, Lewis & Bockius LLP

Donald J. Bird
Registration No. 25,323

Dated: **October 15, 2008**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: 202-739-3000
Fax: 202-739-3001

PTO/SB/06 (12-04)

Filing Date: 10/15/08

Approved for use through 7/31/2006. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number
12/285,887

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	23 minus 20 =	3	x$26		OR	x$52	156
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
			TOTAL			TOTAL	1246

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET
Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
12/285,887	10/15/2008

Applicant(s)

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
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Total Indep	2					
Total Depend	40					
Total Claims	42					

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/285,887	10/15/2008	1617	0.00	056291-5004-02	23	2

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FILING RECEIPT

OC000000032935419

Date Mailed: 11/04/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/872,784 06/22/2004

Foreign Applications

UNITED KINGDOM 0008837.7 04/12/2000
UNITED KINGDOM 0000313.7 01/10/2000

If Required, Foreign Filing License Granted: 11/03/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/285,887**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Formulation

Preliminary Class

514

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	056291-5004-02

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FORMALITIES LETTER

OC000000032935420

Date Mailed: 11/04/2008

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**330** to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*

The application is informal since it does not comply with the regulations for the reason(s) indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The application contains drawings, but the specification does not contain a brief description of the several views of the drawings as required by 37 CFR 1.74 and 37 CFR 1.77(b)(7).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $**156** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**130** for a non-small entity, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**1376** for a non-small entity
- $**330** Statutory basic filing fee.
- $**130** Surcharge.
- The application search fee has not been paid. Applicant must submit $**540** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $**220** to complete the examination fee for a non-small entity.
- Total additional claim fee(s) for this application is $**156**
  - $**156** for **3** total claims over 20.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/tnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	056291-5004-02

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

IMPROPER CPOA LETTER

Date Mailed: 11/04/2008

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the Power of Attorney filed 10/15/2008. The Power of Attorney in this application is not accepted for the reason(s) listed below:

- The Power of Attorney you provided did not comply with the new Power of Attorney rules that became effective on June 25, 2004. See 37 CFR 1.32.

/tnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT
Attorney Docket No. **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1199**
John R. EVANS *et al.*	)	
Application No.: **12/285,887**	)	Group Art Unit: **1617**
Filed: **October 15, 2008**	)	Prior Examiner: **San-Ming R. Hui**
FOR: **FORMULATION**	)	Date: **June 4, 2009**

SECOND PRELIMINARY AMENDMENT

Prior to calculation of the excess claims fee and examination on the merits, please amend the claims of the above-referenced application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

IN THE CLAIMS:

This listing of claims will replace all prior versions and listing of claims in this application.

Listing of the claims:

Claim 1 (**original**): A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ for at least 2 weeks.

Claim 2 (**original**): A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks.

Claim 3 (**original**): A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks.

Claim 4 (**original**): A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

Claim 5 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim ~~4 to 4~~ 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

Claim 6 (**original**): A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

Claim 7 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim ~~4 any claim from 1 to 6~~ which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

Claim 8 (**original**): A pharmaceutical formulation as claimed in claim 7 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

Claim 9 (**original**): A pharmaceutical formulation as claimed in claim 7 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

Claim 10 (**original**): A pharmaceutical formulation as claimed in claim 7 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

Claim 11 (**original**): A pharmaceutical formulation as claimed in claim 7 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

Claim 12 (**original**): A pharmaceutical formulation as claimed in claim 7 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

Claim 13 (**original**): A pharmaceutical formulation as claimed in claim 7 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

Claim 14 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~any claim from 1 to 13~~ wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

Claim 15 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~any claim from 1 to 14~~ wherein the pharmaceutically-acceptable non-aqueous ester solvent

is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

Claim 16 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~any claim from 1 to 15~~ wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

Claim 17 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~any claim from 1 to 16~~ wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

Claim 18 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~any claim from 1 to 13~~ wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

Claim 19 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~claim 18~~ wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

Claim 20 (**currently amended**): A pharmaceutical formulation as claimed in claim 1 or claim 4 ~~any of claims 1-19~~ wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

Claim 21 (**currently amended**): A method of treating a benign or malignant diseases of the breast or reproductive tract by administration to a human in need of such treatment by intramuscular a pharmaceutical formulation as claimed in claim 1 or claim 4 ~~claims 1 to 19~~.

Claim 22 (**original**): A method as claimed in claim 21 for treating breast cancer.

Claim 23 (**original**): A syringe or vial containing a pharmaceutical formulation as defined in claim 20.

REMARKS

Claim Amendments

The claims have been amended to remove improper multiple dependencies.

These amendments have been made without waiver or prejudice to Applicants' right to prosecute any subject matter deleted thereby in one or more continuing applications. Following entry of these amendments, claims 1-23 remain pending in this application.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: June 4, 2009
By: /Donald Bird/

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

PATENT
Attorney Docket No. **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1199**
John R. EVANS *et al.*	)	
Application No.: **12/285,887**	)	Group Art Unit: **1617**
Filed: **October 15, 2008**	)	Prior Examiner: **San-Ming R. Hui**
FOR: **FORMULATION**	)	Date: **June 4, 2009**

STATEMENT ACCOMPANYING SUBSTITUTE SPECIFICATION

In response to the Notice to File Missing Requirements, attached are a clean copy and a marked up copy of the substitute specification in which headings have been inserted. Both copies contain the amendments that are set forth in the Preliminary Amendment filed on October 15, 2008. The attached copies of the substitute specification do not include prohibited new matter. In particular, referring to the "marked up" copy:

- At page 1, the text under CROSS-REFERENCE TO RELATED APPLICATIONS was previously inserted by the Preliminary Amendment of October 15, 2008.
- At page 1, the deleted text under "Field of the Invention" has been copied to page 6 under SUMMARY OF THE INVENTION.
- At page 6, the text under SUMMARY OF THE INVENTION is copied from the original specification at page 1, lines 3-9.
- At page 6, the text under BRIEF DESCRIPTION OF THE DRAWING is copied from the original specification at page 15, lines 3-5.
- The claims in this substitute specification are as originally presented. However, the Examiner's attention is drawn to the accompanying Second Preliminary Amendment wherein the claims are amended to remove improper multiple dependencies.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time

under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **June 4, 2009**
By: /Donald Bird/

Donald J. Bird
Registration No.25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000

FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation Application of copending U.S. Patent Application No. 10/872,784, filed June 22, 2004, which claims benefit of U.S. Patent Application No. 09/756,291, filed January 9, 2001 which claims the benefit of Great Britain Application No. 0008837.7 filed April 12, 2000 and Great Britain Application No. 0000313.7, filed January 10, 2000, all of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Description of the Related Art

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be “pure” antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for

the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

SUMMARY OF THE INVENTION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 below, and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits.

DETAILED DESCRIPTION OF THE INVENTION

Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20
Miglyol 810	3.06

Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly

lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibly other organic solvents, for example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-

25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and difficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still achieved by the formulation of the invention.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v							
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols

	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site

	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+

0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

A further feature of the invention is a method of treating a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

Preferably 5ml of the intramuscular injection is administered.

A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably treating breast cancer.

Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary

pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol

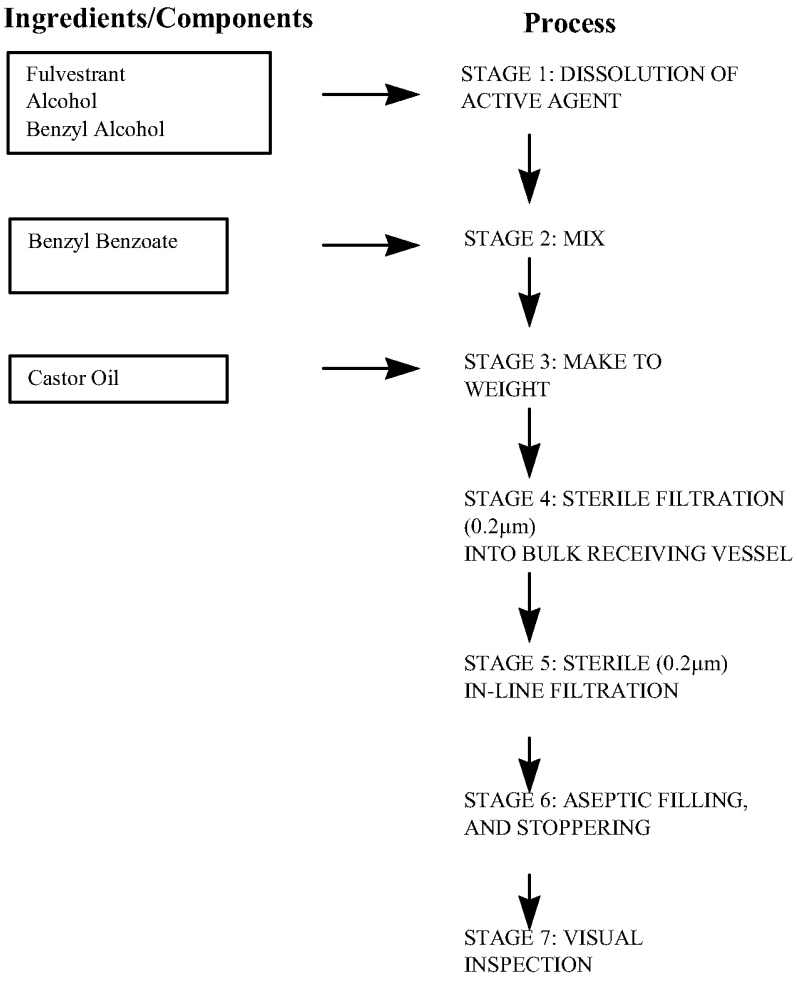
10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ for at least 2 weeks.

2. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks.

3. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks.

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7. A pharmaceutical formulation as claimed in any claim from 1 to 6 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

8. A pharmaceutical formulation as claimed in claim 7 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

9. A pharmaceutical formulation as claimed in claim 7 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 7 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

11. A pharmaceutical formulation as claimed in claim 7 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 7 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 7 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

15. A pharmaceutical formulation as claimed in any claim from 1 to 14 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

16. A pharmaceutical formulation as claimed in any claim from 1 to 15 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

17. A pharmaceutical formulation as claimed in any claim from 1 to 16 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

18. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

19. A pharmaceutical formulation as claimed in claim 18 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

20. A pharmaceutical formulation as claimed in any of claims 1-19 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

21. A method of treating a benign or malignant diseases of the breast or reproductive tract by administration to a human in need of such treatment by intramuscular a pharmaceutical formulation as claimed in claims 1 to 19.

22. A method as claimed in claim 21 for treating breast cancer.

23. A syringe or vial containing a pharmaceutical formulation as defined in claim 20.

ABSTRACT OF THE DISCLOSURE

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

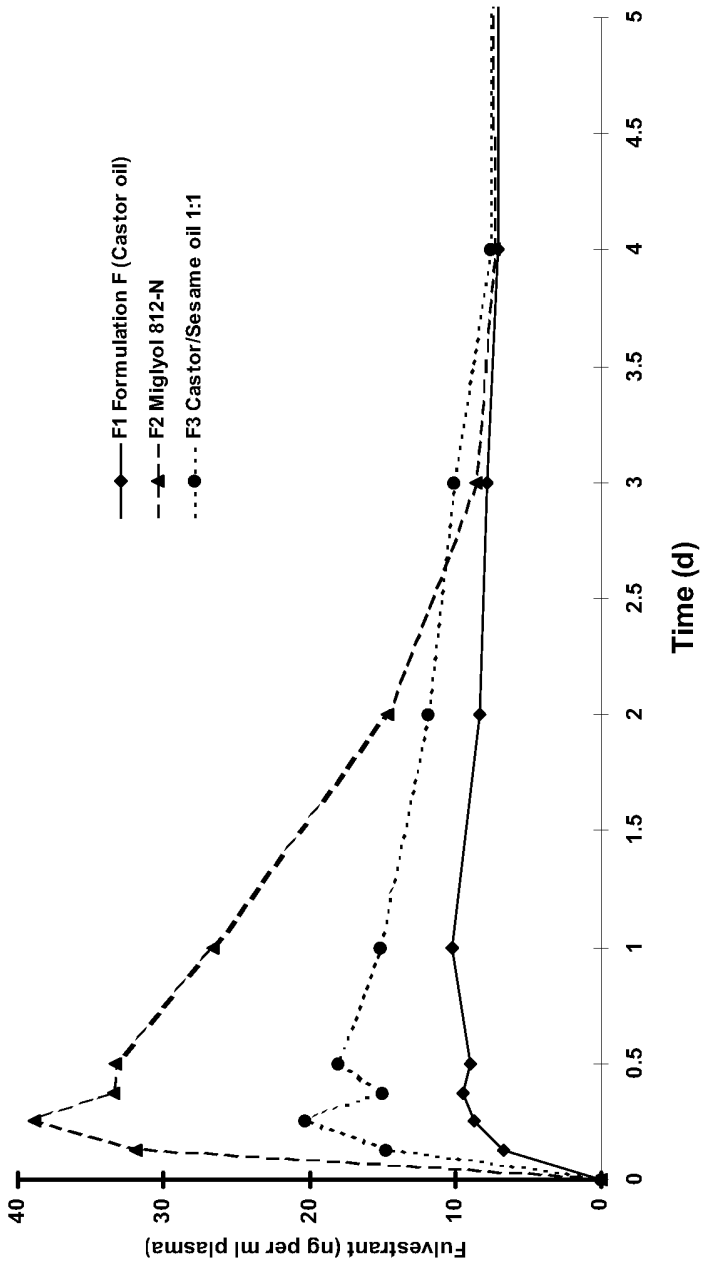
F1 Formulation F (Castor oil)
F2 Miglyol 812-N
F3 Castor/Sesame oil 1:1
Fulvestrant (ng per ml plasma)
Time (d)
0
10
20
30
40
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

Figure 1

Electronic Patent Application Fee Transmittal

Application Number:	12285887
Filing Date:	15-Oct-2008
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Filer:	Donald J. Bird
Attorney Docket Number:	056291-5004-02

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Claims in excess of 20	1202	22	52	1144
Independent claims in excess of 3	1201	2	220	440
Multiple dependent claims	1203	1	390	390

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 5 months with $0 paid	1255	1	2350	2350
Miscellaneous:				
		Total in USD ($)		**5544**

Electronic Acknowledgement Receipt

EFS ID:	5447464
Application Number:	12285887
International Application Number:	
Confirmation Number:	1199
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	09629
Filer:	Donald J. Bird
Filer Authorized By:	
Attorney Docket Number:	056291-5004-02
Receipt Date:	04-JUN-2009
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Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5544
RAM confirmation Number	215
Deposit Account	500310
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	056291-5004-02-IDS-First.pdf	81302 eade4c534e276bda9fa6f9e5b4e8332d9142e0aa	no	2
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed (SB/08)	056291-5004-02-1449-First.pdf	116751 e68383a4eeb651aaf482cbba6d53e829038a4d20	no	3
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	WO99027906.pdf	1201771 17eb0e2105e6de09d3b59735d456b173d15d799f	no	30
Warnings:					
Information:					
4	NPL Documents	PharmaceuticalDosageForms.pdf	321460 39ff9c71d0af795f5437c1a25f3481319563e66f	no	5
Warnings:					
Information:					
5	Transmittal Letter	056291-5004-02-IDS-Second.pdf	81796 fd36687d33e20f7fd5ff580e7099a596bc13416e	no	2
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Filed (SB/08)	IDSonControlledConfidentialNonCommercialTesting.pdf	792753 cb3373ff7c2ce4bc041ffd0dad5f368f09c2c590	no	19
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7	Transmittal Letter	056291-5004-02-IDS-Third.pdf	82365 d9be9d39c492d49ab6b6d49daa15f9c47d949b80	no	2
Warnings:					
Information:					
8	Information Disclosure Statement (IDS) Filed (SB/08)	056291-5004-02-1449-Third.pdf	113011 9e24bc0dd8cf2f5039110bd1967ef93c8b7c1038	no	1
Warnings:					

Information:					
This is not an USPTO supplied IDS fillable form					
9	Foreign Reference	Third-IDS-Attachment_1_EP1250138B1.pdf	1033234 81ddbbf4194370660cd8dc7eddbe333789fcfe55	no	22
Warnings:					
Information:					
10	Foreign Reference	Third-IDS-Attachment_2_EP1250138B1-Opposition.pdf	13564969 40565840d23255482e222a3baf07ab64d13d70a3	no	323
Warnings:					
Information:					
11	Foreign Reference	Third-IDS-Attachment_3_EPSearchReport.pdf	302425 dca31854f20a13359152eac5a9511c65b2d48cd5	no	10
Warnings:					
Information:					
12		056291-5004-02-PreliminaryAmendment.pdf	93701 ca09efc3357d1e9ee8a65e5db4da159c49400150	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
13	Applicant Response to Pre-Exam Formalities Notice	056291-5004-02-StatementAccompanying-SubstituteSpecification.pdf	92679 22f9f3beba00152b5b15cbb47600c4cea46332b0	no	2
Warnings:					
Information:					
14		056291-5004-02-SubstituteSpecification-CleanCopy.pdf	109710 5e1d509a92fd52412d6fa8ccd3b6124be3daf91f	yes	25

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	20

	Claims		21	23	
	Abstract		24	24	
	Drawings-only black and white line drawings		25	25	
Warnings:					
Information:					
15	Specification	056291-5004-02-SubstituteSpecification-MarkedCopy.pdf	111551 eaca016da35e65b59d55b4252f29a81707b065b5	no	25
Warnings:					
Information:					
16	Fee Worksheet (PTO-875)	fee-info.pdf	42584 cd28591b73ad539e0e4d6b6b16512f68460b0231	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	18142062		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT
Attorney Docket No. **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1199**
John R. EVANS *et al.*	)	
Application No.: **12/285,887**	)	Group Art Unit: **1617**
Filed: **October 15, 2008**	)	Examiner: **Unassigned**
FOR: **FORMULATION**	)	Date: **June 4, 2009**

FIRST INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicants request that the Examiner consider this Information Disclosure Statement and the documents listed on the attached Form PTO-1449. To the best of the undersigned's knowledge, this Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits in the above-referenced application. Accordingly, Applicants do not believe that a fee is due for filing this Information Disclosure Statement.

With the exception of documents 38 and 65, copies of the listed documents were previously submitted or cited by the Examiner in parent Application No. 10/872,784. A copy of each of documents 38 and 65 are attached. Applicants respectfully request that the Examiner initial and return the Form PTO-1449, indicating that the information has been considered and made of record herein.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." Applicants reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required,

including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **June 4, 2009**
By: /Donald Bird/

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000

PATENT
ATTORNEY DOCKET NO.: 096291-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:

EVANS et al.

Appln. No.: 09/756,291

Filed: January 9, 2001

FOR: FORMULATION

Group Art Unit: 1617

Examiner: Hui, San-ming

September 13, 2002

Commissioner of Patents
Washington, D.C. 20231

Sir:

SECOND INFORMATION DISCLOSURE STATEMENT

Applicant wishes to make of record the following circumstances regarding the controlled, confidential and non-commercial testing of compositions meeting the definition of "pharmaceutical formulation", as used in the present method of treatment claims, which was carried out in the United States more than one year before the filing date of the present application in preparation for and during the testing (IND) phase of the regulatory review of such formulation by the FDA.

1. The elected invention as presently claimed is directed toward a method for treating a benign or malignant disease of the breast or reproductive tract of a human by intra-muscular injection of a particular pharmaceutical formulation comprising the active drug fulvestrant in a vehicle comprising ricinoleate, a pharmaceutically-acceptable alcohol, and a pharmaceutically-acceptable non-aqueous ester solvent miscible in ricinoleate, as detailed in the claims.

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2. Fulvestrant is the international non-proprietary (generic) name for the compound 7-alpha-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3-5(10)-triene-3,17-beta-diol, which compound is encompassed by claims of U.S. Patent No. 4,659,516 issued to Bowler *et al.* in 1987 (hereinafter the "Bowler '516 patent").

3. The present specification acknowledges that fulvestrant is included among the steroid derivatives disclosed in European Patent Application No. 0 138 504 (corresponding to the Bowler '516 patent) as being effective antioestrogenic agents. The Bowler '516 patent notes at the bottom of column 7 that compositions of the disclosed steroid derivatives may be in a form suitable for oral or parenteral administration, and that compounds having antioestrogenic effect may have value in the treatment of, *e.g.*, anovulatory infertility, breast tumors and menstrual disorders.

4. However, certain characteristics of fulvestrant make it very difficult to formulate a pharmaceutically acceptable and effective composition for administration to humans. In particular, fulvestrant is an extremely lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low, placing severe limitations on the manner and mechanism by which it can be administered.

5. Subsequent to grant of the Bowler '516 patent, applicants developed an injectable extended release formulation of fulvestrant by which it became feasible to effectively utilize the known pharmacological properties of fulvestrant in the treatment of benign or malignant diseases of the breast or reproductive tract in humans, as presently claimed. This injectable extended release formulation of fulvestrant was subjected to extensive *in*

vitro and *in vivo* testing in animals, and eventually in clinical trials as detailed below, leading up to the first FDA approval of this formulation in April 2002.

6. In brief chronology, fulvestrant was initially put into development by Imperial Chemical Industries PLC (hereinafter "ICI"), under the product designation ICI 182,780. Development of fulvestrant was continued by Zeneca Limited (formed from ICI in 1993) under the product designation ZD9238. By December 6, 1996, preliminary testing of an injectable formulation containing fulvestrant as active ingredient had progressed to the point that an IND (Investigational New Drug) application was filed with the FDA for FASLODEX® (fulvestrant) Injection. As of the January 5, 1997 effective date of the IND application, clinical testing could, for the first time, commence in human subjects in the United States.

7. Clinical testing under the IND continued on behalf of AstraZeneca (formed by merger in 1999) until it was believed that sufficient evidence of safety and efficacy of the formulation had been obtained, and on March 28, 2001 an NDA (New Drug Application) was submitted to the FDA. Meanwhile, the subject application for patent, Application No. 09/756,291, was filed in the United States on January 9, 2001, claiming priority from GB Application 0000313.7, filed January 10, 2000, and GB Application 0008837.7, filed April 12, 2000. Thereafter, on April 25, 2002, the NDA for the Faslodex (injectable fulvestrant formulation) was approved by the FDA, whereupon Faslodex was approved for commercial marketing for the treatment of certain breast cancers.

8. The injectable fulvestrant formulation constituting Faslodex comes within the definition of "pharmaceutical formulation" as used in the method of treatment claims presently

pending in this application. The April 25, 2002 approval date constitutes the earliest possible date for commercial marketing in the United States of a formulation for use in accordance with the present claims.

9. This FDA approval came after the present application was filed, and was the culmination of many years of testing and gathering of data on the injectable formulation of fulvestrant (ICI 182,780 or ZD9238), both in the United States and abroad, in animals and eventually in human clinical trials. As will be evident below, all such testing in the United States more than one year before this application was filed was carried out under agreements which imposed obligations of confidentiality on the involved institutions and/or investigators, gave AstraZeneca strict control over the permitted use and disposition of the test samples of formulation, and provided that AstraZeneca was entitled to all information or data derived from the testing.[1] Moreover, all persons enrolled in the clinical trials were advised of the experimental nature of the formulation, and acknowledged this in signed informed consent forms as a precondition to their enrollment. AstraZeneca received no payment for the samples, and was not otherwise compensated for the use of these samples in the clinical trials. Under these conditions and the applicable case law discussed later below, these tests of the fulvestrant formulation in the United States did not constitute a "public use" under 35 U.S.C. § 102(b) of the present invention because the tests were carried out under strict obligations of confidentiality, and the tests and the use and disposition of the formulation, remained

[1] Reference to AstraZeneca hereinafter should be understood to refer to AstraZeneca and/or its predecessors in interest, ICI and Zeneca, unless the context indicates otherwise.

under the control of AstraZeneca throughout the entire period. These tests did not place the formulation in the public domain or cause the public to believe that the formulation of the invention was freely available, and certainly did not constitute a commercial exploitation of the invention more than one year before this application was filed.

10. Prior to the January 5, 1997 effective date of the IND application, all testing of fulvestrant formulation in the United States was necessarily carried out *in vitro* or in animals, and therefore cannot come within the scope of the present method of treatment claims. Nevertheless, it should be noted that all such testing was carried out under strict conditions of confidentiality and limitations of use imposed by a Statement of Proposed Investigation (SOPI) form that each investigator was required to sign as a condition to receiving samples of fulvestrant formulation.

11. The SOPI forms used by ICI in the early 1990s required a statement of proposed use of the material (necessarily not including any use in humans) that had to be approved by ICI, and stated just above the required signature of the investigator:

"If samples are supplied, I undertake:-

1. to make available all results to ICI;
2. that the results will not be submitted for publication or disclosed in any other way prior to disclosure to ICI;
3. to use the samples only for the purposes described above and not to pass the samples or any portion thereof to any investigators for any other purpose;
4. not to use the samples for any commercial purpose or for any study requested by a commercial organization."

12. The SOPI forms used by Zeneca and AstraZeneca (even after the effective date of the IND, for any samples provided to investigators outside of formal protocols for clinical or compassionate use trials discussed below) similarly required a statement of proposed use of the material that had to be approved by Zeneca or AstraZeneca, and explicitly stated, "Laboratory studies/tests on animals only. (Not for human use)." Again, just above the signature of the investigator, the following undertaking was printed on each form:

"1. All results acquired as a direct result of the use of the sample(s) will be promptly furnished to AstraZeneca.

2. The results will not be submitted for publication or disclosed in any other way without prior consent from AstraZeneca, which will not be unreasonably withheld.

3. The sample(s) will only be used for the purpose described above and shall not be passed to a third party. Any unused material will be returned to AstraZeneca.

4. The sample(s) will not be used to support the development of any commercial product containing the compound(s) supplied by AstraZeneca.

5. AstraZeneca shall be granted first option of a license to all rights in any discoveries or inventions made as a direct result of the investigations described above (whether patentable or not). In particular, the option will include an option for a license under any patents and patent applications relating to the use of the sample(s).

6. AstraZeneca requires assurance from all external investigators that all studies carried out on behalf of AstraZeneca and/or involving AstraZeneca compounds are carried out in compliance with all animal welfare legislation, regulations and policies applicable in that country/state. Please let us have your confirmation in writing that this is the case. We would also like to receive any additional

information on your in-house animal welfare arrangements which you are able to provide."

13. It is understood that no investigator receiving fulvestrant formulation pursuant to a SOPI, at least in the United States and prior to the filing of the present application for patent, was informed of the components and/or proportions thereof constituting the injectable vehicle in which the fulvestrant was carried, and that no investigator publication of results approved by AstraZeneca included such a disclosure.

14. Two clinical studies involving Faslodex were carried out at least in part in the United States prior to the filing date of the present application for patent.

- Clinical Study 9238IL/0021 began, in the United States, in April 1997 and extended to June 2000; was carried out in 69 centers involving 414 patients; and had the objective of comparing the effect, in terms of time to progression, of two doses of Faslodex (125 and 250 mg) with one dose of Arimidex (1 mg) in postmenopausal women with advanced breast cancer.

- Clinical Study 9238IL/0025 began, in the United States, in November 1998 and extended to July 2001; was carried out in 32 centers involving 51 patients; and had the objective of comparing the effect, in terms of time to progression, of Faslodex (250 mg) with Nolvadex (20 mg) as first-line therapy in postmenopausal women with advanced breast cancer.

15. Each clinical study was carried out under a Clinical Study Agreement entered into by each Institution and Investigator taking part in the study.

16. A representative Clinical Study Agreement for Clinical Study 9238IL/0021 provided in relevant part:

> "The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol entitled "A Double-blind, Randomized, Multicenter Trial comparing the Efficacy and Tolerability of 125 and 250 mg of FASLODEX™ (Long-acting ICI 182,780) With 1 mg ARIMIDEX™ (Anastrozole) in Postmenopausal Women With Advanced Breast Cancer" (hereinafter referred to as "Protocol"). Institution shall use its best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."
>
> * * * * *
>
> "ZENECA reserves the right to terminate this Agreement and Study at any time in its sole discretion upon thirty (30) days prior written notice. However, ZENECA may terminate this agreement upon five (5) days written notice for safety, regulatory or ethical reasons. In the event of termination, all unused Study materials shall be returned to ZENECA and ZENECA shall reimburse Institution for all actual costs reasonably incurred up until the effective termination date."
>
> * * * * *
>
> "All rights to all data, inventions or discoveries Institution may make or conceive in the course of their work for ZENECA in their performance under this Agreement and using product in accordance with the detailed protocol provided by ZENECA will be the property of ZENECA and will be assigned to ZENECA, and Institution will assist ZENECA, at ZENECA's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries in any country which ZENECA at ZENECA's option, desires to obtain patent protection. All control of and decisions regarding such patent filings and prosecution, whether U.S. or foreign, and all costs and fees associated therewith, shall be exercised and/or borne by ZENECA."

* * * * *

"It may be necessary for Zeneca to disclose to Institution certain information considered proprietary or confidential (hereinafter 'Confidential Information') to aid Institution in effecting or completing their performance under this Agreement. Institution agrees to maintain in confidence all Confidential Information Institution obtains from ZENECA relating to this Agreement and not to disclose any of said Confidential Information to a third party for a period of three (3) years after the termination of this Agreement without the prior written consent of ZENECA. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Institution obtain from some third party not under any obligation to ZENECA with respect to such information, or (iv) information which Institution already have in their possession, prior to any disclosure by ZENECA, as evidenced by written records, (v) is independently developed by Institution or (vi) is required by law or regulation to be disclosed, provided, however, that Institution notifies and consults with Zeneca prior to such disclosure.

"Subject to the provisions of confidentiality set forth in Section 6(d) above, ZENECA agrees to grant Institution the right to publish its findings in the scientific literature, provided that ZENECA shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. Upon request by ZENECA, in order to protect intellectual property rights, Institution agrees to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which ZENECA receives such final draft manuscripts. Institution agrees to implement any reasonable suggestions made to preserve ZENECA's

right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agrees to take appropriate cognizance of any other suggestions by ZENECA before any disclosure for publication or presentation."

17. A representative Clinical Study Agreement for Clinical Study 9238IL/0025 similarly provided in relevant part:

"The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol which is attached hereto as Exhibit A and incorporated herein by reference. Institution and Investigator shall use their best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."

* * * * *

"Zeneca reserves the right to terminate this Agreement and Study at any time in its sole discretion upon five (5) days prior written notice. In the event of termination, all unused Study materials shall be returned to Zeneca and Zeneca shall reimburse Institution and Investigator for all actual costs reasonably incurred up until the effective termination date."

* * * * *

"All rights to all data, inventions or discoveries Institution and Investigator may make or conceive in the course of their work for Zeneca in their performance under this Agreement will be the property of Zeneca and will be assigned to Zeneca, and Institution and Investigator will assist Zeneca, at Zeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries."

* * * * *

"It may be necessary for Zeneca to disclose to Investigator and Institution certain information considered proprietary or confidential (hereinafter "Confidential

Information") to aid Investigator and Institution in effecting or completing their performance under this Agreement. Confidential Information shall also include Study data; however, Investigator's and Institution's right to publish pursuant to Section (d) below* shall not be affected by this provision. Investigator and Institution agree to maintain in confidence all Confidential Information Investigator and Institution obtain from Zeneca relating to this Agreement and not to disclose any of said Confidential Information to a third party without the prior written consent of Zeneca. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Investigator and Institution obtain from some third party not under any obligation to Zeneca with respect to such information, or (iv) information which Investigator and Institution already have in their possession, prior to any disclosure by Zeneca, as evidenced by written records.

"Nothing herein shall prevent Investigator and Institution from complying with the legal obligation to disclose Confidential Information so long as Investigator and Institution (i) provide Zeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) take reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) afford Zeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator and Institution have sought to resist disclosure) or obtain protection for the information disclosed."

* * * * *

*[(d)] "Subject to the provisions of confidentiality set forth in Section 6(c) above, Zeneca agrees to grant Investigator and Institution the right to publish their findings in the scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Investigator and

Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator and Institution agree to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which Zeneca receives such final draft manuscripts. Investigator and Institution agree to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agree to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

* * * * *

"Zeneca shall be entitled to make copies, at Zeneca's expense, of any and all documents and data generated from the Study. In addition, Institution and Investigator agree to allow Zeneca to audit the Study records (including administrative files and source documents such as hospital charts, office records and written results of laboratory and diagnostic tests) of Institution and Investigator at mutually convenient times.

18. An additional clinical study involving Faslodex was commenced in the United States more than one year prior to the filing date of the present application for patent, being Clinical Study 9238IL/0037, a compassionate-use trial under a protocol initially entitled "An Open-label, Treatment-use Protocol of 250 mg of FASLODEX™ (Long-acting ICI 182,780) in Postmenopausal Women With Advanced Breast Cancer." It is understood that as of one year prior to the filing date of this application, seven subjects had been enrolled in Clinical Study 9238IL/0037.

19. A "Confidentiality and Proprietary Rights Agreement" was entered into by each Investigator prior to his involvement in Clinical Study 9238IL/0037, in which the Investigator acknowledged that "he will have access to and obtain knowledge of certain proprietary and confidential Information of Zeneca and that as a condition of receiving such information" the parties agreed, in part as here relevant:

"1. 'Confidential Information' shall mean all information (a) disclosed by Zeneca to Investigator, either orally or in writing or (b) obtained by the Investigator from a third party or any other source, regarding the protocol entitled 'An Open-label, Treatment-use Protocol of 250 mg of FASLODEX™ (Long-acting ICI 182,780) in Postmenopausal Women With Advanced Breast Cancer, Study No. 9238IL/0037' ('Study')

"Confidential Information shall not include information that: (i) was already in the possession of Investigator before disclosure thereof by Zeneca to Investigator as evidenced by Investigator's written records (ii) is independently developed by Investigator as evidenced by Investigator's written records, (iii) is or becomes publicly available through no fault of Investigator, or (iv) is obtained by Investigator from a third party under no obligation not to disclose same.

"Nothing herein shall prevent Investigator from complying with a legal obligation to disclose Confidential Information so long as Investigator (i) provides Zeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) takes reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) affords Zeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator has sought to resist disclosure) or obtain protection for the Information disclosed.

"2. The purpose of the disclosure of Confidential Information is to allow Investigator to participate in the Treatment-use Protocol.

"3. Investigator agrees to maintain in strictest confidence and to take all reasonable steps to maintain the confidentiality of the Confidential Information. Investigator also agrees not to disclose Confidential Information to any third party, and to use Confidential Information only for the purposes stated in paragraph 2 of this Agreement.

"4. Investigator recognizes that all documents and records received by Investigator from Zeneca and all copies of such records and documents shall be Zeneca's property exclusively. The Investigator shall at all times keep all such documents, records and copies of documents and records in Investigator's custody and subject to Investigator's control and shall surrender the same upon request by Zeneca.

"5. Investigator shall not disclose any Confidential Information to any of its employees, except employees of Investigator who have a need to know the Confidential Information for the purposes stated in paragraph 2 of this Agreement and who have assumed an obligation to maintain Zeneca's Confidential Information in confidence at least to the extent that Investigator is bound hereunder. Investigator shall advise each such employee of the confidential nature of the Confidential Information received from Zeneca and the existence and importance of the confidentiality provisions of this Agreement and shall be responsible for ensuring that such employees maintain the Confidential Information in confidence in accordance with the terms of this Agreement.

"6. Because of the unique nature of the Confidential Information, Investigator understands and agrees that Zeneca will suffer irreparable harm in the event that Investigator fails to comply with any of its obligations contained hereinabove and that monetary damages will be inadequate to compensate Zeneca for such breach. Accordingly, Investigator agrees that Zeneca shall have the right to seek immediate injunctive relief to enforce the confidentiality obligations contained herein.

"7. All rights to all data, inventions or discoveries Investigator may make or conceive in the course of Investigator participation in the Study will be the property of Zeneca and will be assigned to Zeneca, and Investigator will assist Zeneca, at Zeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries. Investigator agrees to make no claim which will restrict the rights of Zeneca to use and disclose to others any information, knowledge, and ideas which are disclosed to Zeneca by Investigator in the course of performance of the Study.

"8. Subject to the provisions of confidentiality set forth herein, Zeneca agrees to grant Investigator the right to publish his findings in the scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored by Investigator or by anyone in his research group and which are based in whole or in part on research conducted pursuant to this Study. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator agrees to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which Zeneca receives such final draft manuscripts. Investigator agrees to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator agrees to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

20. The Protocols referenced with respect to the above-noted Studies No. 9238IL/0021, No. 9238IL/0025 and No. 9238IL/0037 provided details of, *inter alia*, the:

- criteria for the selection and screening for eligibility of subjects for entry into the trial, as well as exclusion criteria;

- route, dose and regimen for administration of the respective drugs to individual subjects;
- procedures for drug accountability, including maintenance of accurate records on receipt and disposition of investigational materials, and return or destruction of any unused drug;
- frequency and procedures for clinical and laboratory evaluations;
- regular recordation of data on case report forms, record retention and submission of records to AstraZeneca; and
- trial monitoring and data verification by representatives of AstraZeneca.

21. These Protocols furthermore required that each subject be given appropriate information on the treatment prior to its commencement, including the experimental aspects of the treatment and the risks involved, and sign an informed consent form approved by AstraZeneca, and conforming to the requirements of 21 C.F.R. 50.20 *et seq.* , which requires as a basic element of informed consent, that each subject be provided with, *inter alia*, a "statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental." 21 C.F.R. 50.25(a)(1).

In evaluating the above circumstances in context of 35 U.S.C. § 102(b), the Examiner's attention is called to MPEP ¶ 2133.03 "Rejections Based on 'Public Use' or 'On Sale', and particularly MPEP ¶ 2133.03(a) "Public Use", section *B.* headed "*Use by Third*

Parties Deriving the Invention from Applicant." It is respectfully submitted that the above circumstances *do not* constitute a "public use" of the presently claimed invention under the criteria set forth in the MPEP, and as established by decisions of the Federal Circuit, because of the strict confidentiality and control imposed and maintained by AstraZeneca throughout the relevant trial periods. MPEP ¶ 2133.03(a)*B*. provides:

> **An Invention Is in Public Use If the Inventor Allows Another To Use the Invention Without Restriction or Obligation of Secrecy**
>
> "Public use" of a claimed invention under 35 U.S.C. 102(b) occurs when the inventor allows another person to use the invention without limitation, restriction or obligation of secrecy to the inventor." *In re Smith*, 714 F.2d 1127, 1134, 218 USPQ 976, 983 (Fed. Cir. 1983). The presence or absence of a confidentiality agreement is not itself determinative of the public use issue, but is one factor to be considered along with the time, place, and circumstances of the use which show the amount of control the inventor retained over the invention. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1265, 229 USPQ 805, 809 (Fed. Cir. 1986). See *Ex parte C*, 27 USPQ2d 1492, 1499 (Bd. Pat. App. & Inter. 1992) (Inventor sold inventive soybean seeds to growers who contracted and were paid to plant the seeds to increase stock for later sale. The commercial nature of the use of the seed coupled with the "on-sale" aspects of the contract and apparent lack of confidentiality requirements rose to the level of a "public use" bar.); *Egbert v. Lippmann*, 104 U.S. 333, 336 (1881) (Public use found where inventor allowed another to use inventive corset insert, though hidden from view during use, because he did not impose an obligation of secrecy or restrictions on its use.).

The samples of fulvestrant formulation provided under the SOPI forms was not for human use, and therefore outside of the scope of the present method of use claims. Nevertheless, the tests conducted on these samples by the third party Investigators did not constitute a "public use". Through the SOPI forms, AstraZeneca maintained strict confidentiality over the samples and tests conducted therewith, maintained control over the use and disposition of the samples, and was entitled to all data developed in the course of the

tests. (¶¶ 10-13, *supra*). Moreover, AstraZeneca received no payment or other commercial benefit from providing these samples

Similarly, the three clinical trials or studies conducted in human subjects did not constitute a "public use" under the definition thereof set out in the MPEP as developed by the courts. Prior to the release of any materials or formulations on which to carry out these studies, the institutions and/or investigators involved were required to sign an agreement whereunder strict confidentiality was required, and all information provided to or developed by the institution/investigator during the course of such studies remained or became the property of AstraZeneca. (¶¶ 16, 17 and 19, *supra*). Through the Clinical Study Agreements, and the Protocols under which all three studies were conducted, AstraZeneca maintained full control over the use and disposition of the study materials or formulation that it provided to the institutions/investigators throughout the course of these studies, and the right to receive the data and records that were produced. (¶¶ 16, 17 and 20, *supra*). Moreover, each subject of these studies was fully informed of the experimental nature of the formulation and its use, as acknowledged in signed informed consent forms, and clearly did not have any basis to believe that the formulation or its use in the treatments was in the public domain or otherwise freely available. (¶ 21, *supra*). Again, AstraZeneca received no payment for the formulation used in these studies, and these studies did not constitute a commercial exploitation of the formulation.

Therefore, under the case law as developed by the courts, and its application by the Patent and Trademark Office as set out in the above-quoted paragraph from the MPEP, it is

respectfully submitted that the foregoing circumstances do not constitute a "public use" under 35 U.S.C. § 102(b).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

September 13, 2002 By: _____

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **009629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:

PATENT
Attorney Docket No. **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1199**
John R. EVANS *et al.*	)	
Application No.: **12/285,887**	)	Group Art Unit: **1617**
Filed: **October 15, 2008**	)	Examiner: **Unassigned**
FOR: **FORMULATION**	)	Date: **June 4, 2009**

THIRD INFORMATION DISCLOSURE STATEMENT

UNDER 37 C.F.R. § 1.97(b)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicants request that the Examiner consider this Information Disclosure Statement and the documents listed on the attached Form PTO-1449. To the best of the undersigned's knowledge, this Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits in the above-referenced application. Accordingly, Applicants do not believe that a fee is due for filing this Information Disclosure Statement.

Copies of the listed documents were previously submitted or cited by the Examiner in parent Application No. 10/872,784. Accordingly, no copies of the listed documents are provided herewith. Applicants respectfully request that the Examiner initial and return the Form PTO-1449, indicating that the information has been considered and made of record herein.

Also submitted with this Information Disclosure Statement as Attachments I to III are the following documents: Attachment I: A copy of EP 1250138B1, which is the European Patent that granted on the European counterpart of the subject Application; Attachment II: A copy of documents from the EPO file relating to the European Opposition pending against EP 1250138B1; and Attachment III: A copy the Supplementary European Search Report received by Applicant in European Application 05016921.8, which is a divisional of the application from which EP 1250138B1 granted.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or

constitute "prior art." Applicants reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **June 4, 2009**
Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000

By: /Donald Bird/
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

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INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) PTO Form 1449 June 4, 2009	Attorney Docket No. **056291-5004-02**	Application No. **12/285,887**
	Applicants: **John R. EVANS *et al.***	
	Filing Date: **October 15, 2008**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date
	1.	US 3,164,520	January 5, 1965	Huber			
	2.	US 4,212,863	July 15, 1980	Cornelius			
	3.	US 4,388,307	June 14, 1983	Cavanak			

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation
	4.	EP 0310542A1	April 5, 1989	EPO			Yes

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	5.	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
	6.	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
	7.	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
	8.	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
	9.	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 [pages 238-255 provided] (1998)
	10.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
	11.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
	12.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
	13.	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

Examiner	Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Third IDS

Attachment I

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 250 138 B1

(12) **EUROPEAN PATENT SPECIFICATION**

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(86) International application number:
PCT/GB2001/000049

(87) International publication number:
WO 2001/051056 (19.07.2001 Gazette 2001/29)

(54) **FULVESTRANT FORMULATION**

FULVESTRANT FORMULIERUNG

PREPARATION DE FULVESTRANT

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05016921.8

(73) Proprietor: **AstraZeneca AB**
151 85 Södertälje (SE)

(72) Inventors:
- **EVANS, John, Raymond**
Macclesfield, Cheshire SK10 4TG (GB)
- **GRUNDY, Rosalind, Ursula**
Macclesfield, Cheshire SK10 4TG (GB)

(74) Representative: **Giles, Allen Frank et al**
AstraZeneca AB,
Global Intellectual Property
151 85 Sodertalje (SE)

(56) References cited:
EP-A- 0 346 014 **WO-A-96/19997**
WO-A-97/21440

- **JOHN C. WATERTON; ET AL.: "A Case of Adenomyosis in a Pigtailed Monkey Diagnosed by Magnetic Resonance Imaging and treated with the Novel Pure Antiestrogen, ICI 182,780" LABORATORY ANIMAL SCIENCE, vol. 43, no. 3, 1993, pages 247-251, XP000998289**

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EP 1 250 138 B1

Description

[0001] The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

[0002] Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

[0003] An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

[0004] The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

[0005] Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

[0006] 7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

[0007] Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

[0008] Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

[0009] In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

[0010] European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

[0011] Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

[0012] Currently there are a number of sustained release injectable steroidal formulations which have been com-

mercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

[0013] In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1 week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

		76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
PARABOLAN	Trenbolone										
DELESTROGEN	Estradiol valerate	20mgml^{-1} 40mgml^{-1}	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	250mgml^{-1}	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

[0014] In US 5,183,814 Example 3 an oil based injection formulation of fulvestrant is described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

[0015] Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 -

SOLUBILITY OF FULVESTRANT	
SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20
Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

[0016] As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

[0017] However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

[0018] Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

[0019] The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of $>50mgml^{-1}$ of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$ - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

[0020] Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

[0021] Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

[0022] Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection

comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

[0023] Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

[0024] For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

[0025] Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.
2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.
3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

[0026] It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

[0027] Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

[0028] The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

[0029] The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

[0030] The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

[0031] It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibly other organic solvents, tor example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume

when measured at 15.56°C.

[0032] Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

[0033] It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

[0034] Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

[0035] By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

[0036] We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

[0037] This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and diffcult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.
2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

[0038] It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

[0039] It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

[0040] We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period

can still achieved by the formulation of the invention.

[0041] By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

[0042] By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

[0043] It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

[0044] Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

[0045] Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v					
Ethanol (96%)	5	5	10	10	15	15
Benzyl Alcohol	5	5	5	10	15	15
Benzyl Benzoate		15	15	15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	76	102

[0046] The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols		
	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

(a) **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site							
	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+
0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)							

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

[0047] Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

[0048] Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

[0049] Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

[0050] A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

[0051] A further feature of the invention is the treatment of a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

[0052] Preferably 5ml of the intramuscular injection is administered.

[0053] A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably

treating breast cancer.

[0054] Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

[0055] As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

[0056] In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

[0057] A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

[0058] Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

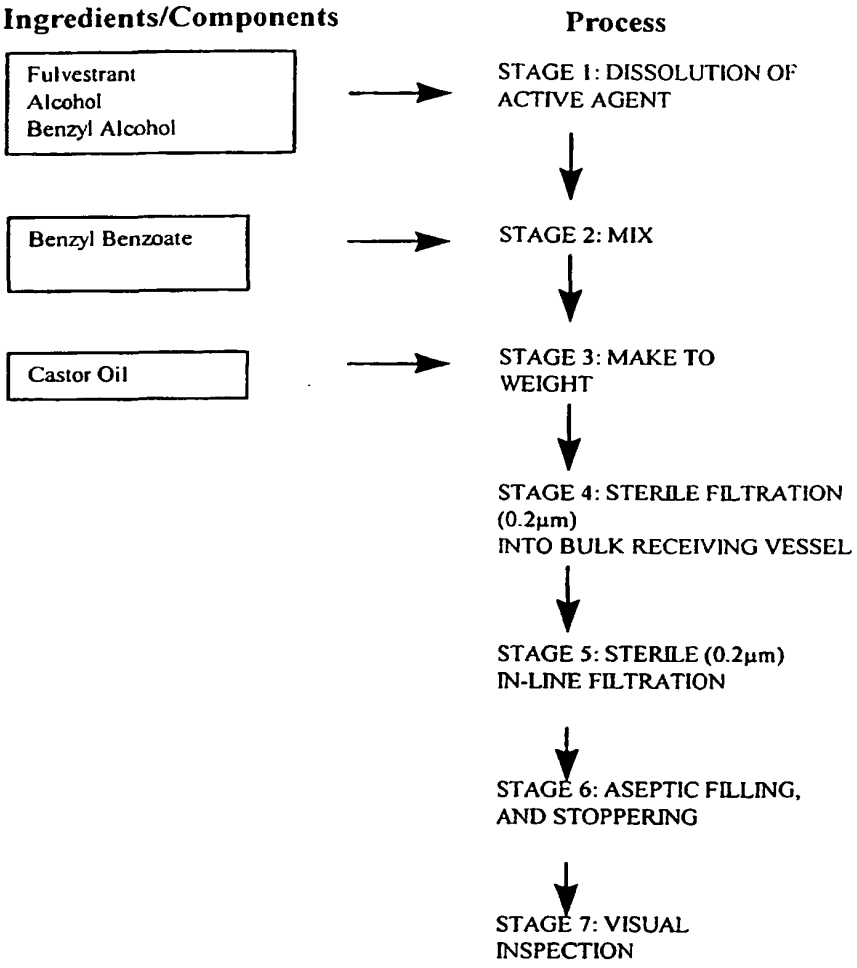
[0059] Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

[0060] Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol
10% weight per volume of ethanol
15% weight per volume of benzyl benzoate
250mg of fulvestrant for each 5ml of finished formulation
and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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[0061]

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Claims

1. A pharmaceutical formulation comprising fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intra-muscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

2. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

3. A pharmaceutical formulation as claimed in claim 1 or 2 wherein the blood plasma fulvestrant concentration attained is at least 2.5ngml^{-1} for at least 2 weeks..

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7. A pharmaceutical formulation as claimed in claim 5 which contains 15-25% w/v of a pharmaceutically acceptable alcohol.

8. A pharmaceutical formulation as claimed in claim 5 which contains 17-23% w/v of a pharmaceutically acceptable alcohol.

9. A pharmaceutical formulation as claimed in any claim from 1 to 8 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 9 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

11. A pharmaceutical formulation as claimed in claim 9 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 9 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 9 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in claim 9 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

15. A pharmaceutical formulation as claimed in claim 9 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

16. A pharmaceutical formulation as claimed in claim 9 which contains 10-25% w/v of a pharmaceutically acceptable

non-aqueous ester solvent.

17. A pharmaceutical formulation as claimed in claim 9 which contains 12-18% w/v of a pharmaceutically acceptable non-aqueous ester solvent.

18. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

19. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

20. A pharmaceutical formulation as claimed in any claim from 1 to 19 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

21. A pharmaceutical formulation as claimed in any claim from 1 to 20 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

22. A pharmaceutical formulation as claimed in any claim from 1 to 21 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

23. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 15-25% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 10-25 % weight of benzyl benzoate in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

24. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 17-23% weight of a pharmaceutically-acceptable alcohol per volume of formulation, 12-18 % weight of benzylbenzoate in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

25. A pharmaceutical formulation according to claim 23 or 24 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

26. A pharmaceutical formulation according to claim 25 wherein the ethanol and benzyl alcohol are present at about equal % weight per volume of formulation.

27. A pharmaceutical formulation as claimed in any claim from 1 to 26 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.

28. A pharmaceutical formulation as claimed in any claim from 1 to 27 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

29. A pharmaceutical formulation as claimed in claim 28 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

30. A pharmaceutical formulation as claimed in any of claims 1-29 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation, and the formulation contains 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

31. A pharmaceutical formulation adapted for intramuscular injection, as defined in any claim from 1 to 30, for use in medical therapy.

32. Use of fulvestrant in the preparation of a pharmaceutical formulation, as defined in any claim from 1 to 30, for the treatment of a benign or malignant disease of the breast or reproductive tract.

33. A syringe or vial containing a pharmaceutical formulation as defined in claim 30.

Patentansprüche

1. Pharmazeutische Formulierung, enthaltend Fulvestrant in einer Ricinoleat-Trägersubstanz, ein pharmazeutisch annehmbares nichtwässriges Esterlösungsmittel und einen pharmazeutisch annehmbaren Alkohol, wobei die Formulierung zur intramuskulären Anwendung und Erzielung einer mindestens 2 Wochen anhaltenden, therapeutisch signifikanten Fulvestrantkonzentration im Blutplasma geeignet ist.

2. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 30 Gew.-% oder weniger eines pharmazeutisch annehmbaren Alkohols und mindestens 1 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer nach Injektion zur Erzielung einer mindestens 2 Wochen anhaltenden, therapeutisch signifikanten Fulvestrantkonzentration im Blutplasma geeigneten Formulierung ausreichende Menge einer Ricinoleat-Trägersubstanz.

3. Pharmazeutische Formulierung nach Anspruch 1 oder 2, bei der die im Blutplasma erzielte Fulvestrantkonzentration mindestens 2 Wochen lang mindestens 2,5 $ngml^{-1}$ beträgt.

4. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 30 Gew.-% oder weniger eines pharmazeutisch annehmbaren Alkohols und mindestens 1 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

5. Pharmazeutische Formulierung nach Anspruch 1 bis 4, die 25% w/v oder weniger eines pharmazeutisch annehmbaren Alkohols enthält.

6. Pharmazeutische Formulierung nach Anspruch 5, die 20% w/v oder weniger eines pharmazeutisch annehmbaren Alkohols enthält.

7. Pharmazeutische Formulierung nach Anspruch 5, die 15-25% w/v eines pharmazeutisch annehmbaren Alkohols enthält.

8. Pharmazeutische Formulierung nach Anspruch 5, die 17-23% w/v eines pharmazeutisch annehmbaren Alkohols enthält.

9. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 8, die 60% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

10. Pharmazeutische Formulierung nach Anspruch 9, die 50% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

11. Pharmazeutische Formulierung nach Anspruch 9, die 45% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

12. Pharmazeutische Formulierung nach Anspruch 9, die 40% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

13. Pharmazeutische Formulierung nach Anspruch 9, die 35% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

14. Pharmazeutische Formulierung nach Anspruch 9, die 30% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

15. Pharmazeutische Formulierung nach Anspruch 9, die 25% w/v oder weniger eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

16. Pharmazeutische Formulierung nach Anspruch 9, die 10-25% w/v eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

17. Pharmazeutische Formulierung nach Anspruch 9, die 12-18% w/v eines pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels enthält.

18. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 15-25 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 10-25 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

19. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 17-23 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 12-18 Gew.-% eines in einer Ricinoleat-Trägersubstanz mischbaren, pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittels, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

20. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 19, bei der es sich bei dem pharmazeutisch annehmbaren Alkohol um ein Gemisch aus Ethanol und Benzylalkohol handelt.

21. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 20, bei der das pharmazeutisch annehmbare nichtwässrige Esterlösungsmittel unter Benzylbenzoat, Ethyloleat, Isopropylmyristat, Isopropylpalmitat oder einem beliebigen Gemisch davon ausgewählt ist.

22. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 21, bei der es sich bei dem pharmazeutisch annehmbaren nichtwässrigen Esterlösungsmittel um Benzylbenzoat handelt.

23. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 15-25 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 10-25 Gew.-% Benzylbenzoat in einer Ricinoleat-Trägersubstanz, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

24. Pharmazeutische Formulierung zur intramuskulären Injektion, enthaltend Fulvestrant, jeweils bezogen auf das Volumen der Formulierung 17-23 Gew.-% eines pharmazeutisch annehmbaren Alkohols und 12-18 Gew.-% Benzylbenzoat in einer Ricinoleat-Trägersubstanz, sowie eine zur Herstellung einer Formulierung mit mindestens 45 $mgml^{-1}$ Fulvestrant ausreichende Menge einer Ricinoleat-Trägersubstanz.

25. Pharmazeutische Formulierung nach Anspruch 23 oder 24, bei der es sich bei dem pharmazeutisch annehmbaren Alkohol um ein Gemisch aus Ethanol und Benzylalkohol handelt.

26. Pharmazeutische Formulierung nach Anspruch 25, bei der der gew.-%ige Anteil an Ethanol und Benzylalkohol pro Volumen Formulierung jeweils etwa gleich ist.

27. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 26, bei der das Gesamtvolumen der Formulierung 6 ml oder weniger und die Fulvestrantkonzentration mindestens 45 $mgml^{-1}$ ausmachen.

28. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 27, bei der die Gesamtmenge an Fulvestrant in der Formulierung 250 mg oder mehr und das Gesamtvolumen der Formulierung 6 ml oder weniger ausmachen.

29. Pharmazeutische Formulierung nach Anspruch 28, bei der die Gesamtmenge an Fulvestrant in der Formulierung 250 mg und das Gesamtvolumen der Formulierung 5 bis 5,25 ml ausmachen.

30. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 29, bei der es sich bei dem pharmazeutisch annehmbaren Alkohol um ein Gemisch von, jeweils bezogen auf das Volumen der Formulierung, 10 Gew.-% Etha-

nol und 10 Gew.-% Benzylalkohol handelt, und die Formulierung pro Volumen 15 Gew.-% Benzylbenzoat enthält, und es sich bei der Ricinoleat-Trägersubstanz um Rizinusöl handelt.

31. Pharmazeutische Formulierung zur intramuskulären Injektion gemäß Definition eines der Ansprüche 1 bis 30 zur Verwendung in der medizinischen Therapie.

32. Verwendung von Fulvestrant bei der Herstellung einer wie in einem der Ansprüche 1 bis 30 definierten pharmazeutischen Formulierung zur Behandlung gutartiger oder bösartiger Erkrankungen der Brust oder des Reproduktionstrakts.

33. Spritze oder Fläschchen, enthaltend eine wie in Anspruch 30 definierte pharmazeutische Formulierung.

Revendications

1. Préparation pharmaceutique comprenant du fulvestrant dans un véhicule de ricinoléate, un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique et un alcool acceptable d'un point de vue pharmaceutique, dans laquelle la préparation est adaptée à une administration intramusculaire et atteint une concentration en fulvestrant dans le plasma sanguin significative d'un point de vue thérapeutique pendant au moins 2 semaines.

2. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 30% ou moins en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, au moins 1% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation qui soit capable, après injection, d'atteindre une concentration en fulvestrant dans le plasma sanguin significative d'un point de vue thérapeutique pendant au moins 2 semaines.

3. Préparation pharmaceutique selon la revendication 1 ou 2, dans laquelle la concentration en fulvestrant dans le plasma sanguin atteinte est de 2,5 $ng.ml^{-1}$ au moins pendant 2 semaines au moins.

4. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 30% ou moins en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, au moins 1% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

5. Préparation pharmaceutique, selon les revendications 1 à 4, qui contient 25% p/v ou moins d'un alcool acceptable d'un point de vue pharmaceutique.

6. Préparation pharmaceutique, selon la revendication 5, qui contient 20% p/v ou moins d'un alcool acceptable d'un point de vue pharmaceutique.

7. Préparation pharmaceutique, selon la revendication 5, qui contient de 15 à 25% p/v d'un alcool acceptable d'un point de vue pharmaceutique.

8. Préparation pharmaceutique, selon la revendication 5, qui contient de 17 à 23% p/v d'un alcool acceptable d'un point de vue pharmaceutique.

9. Préparation pharmaceutique, selon l'une quelconque des revendications 1 à 8, qui contient 60% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

10. Préparation pharmaceutique, selon la revendication 9, qui contient 50% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

11. Préparation pharmaceutique, selon la revendication 9, qui contient 45% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

12. Préparation pharmaceutique, selon la revendication 9, qui contient 40% p/v ou moins d'un solvant d'ester non

aqueux acceptable d'un point de vue pharmaceutique.

13. Préparation pharmaceutique, selon la revendication 9, qui contient 35% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

14. Préparation pharmaceutique, selon la revendication 9, qui contient 30% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

15. Préparation pharmaceutique, selon la revendication 9, qui contient 25% p/v ou moins d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

16. Préparation pharmaceutique, selon la revendication 9, qui contient de 10 à 25% p/v d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

17. Préparation pharmaceutique, selon la revendication 9, qui contient de 12 à 18% p/v d'un solvant d'ester non aqueux acceptable d'un point de vue pharmaceutique.

18. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 15 à 25% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 10 à 25% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

19. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 17 à 23% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 12 à 18% en poids d'un solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique et miscible dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

20. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 19, dans laquelle l'alcool acceptable d'un point de vue pharmaceutique est un mélange d'éthanol et d'alcool benzylique.

21. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 20, dans laquelle le solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique, est choisi parmi : le benzoate de benzyle ; l'oléate d'éthyle ; le myristate d'isopropyle ; le palmitate d'isopropyle ; ou un mélange de n'importe lesquels d'entre eux.

22. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 21, dans laquelle le solvant d'ester non aqueux, acceptable d'un point de vue pharmaceutique, est le benzoate de benzyle.

23. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 15 à 25% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 10 à 25% en poids de benzoate de benzyle, dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

24. Préparation pharmaceutique adaptée à une injection intramusculaire comprenant du fulvestrant, 17 à 23% en poids d'un alcool, acceptable d'un point de vue pharmaceutique, par volume de préparation, 12 à 18% en poids de benzoate de benzyle, dans un véhicule de ricinoléate, par volume de préparation et une quantité suffisante d'un véhicule de ricinoléate, de sorte à élaborer une préparation à 45 $mg.ml^{-1}$ au moins de fulvestrant.

25. Préparation pharmaceutique selon la revendication 23 ou 24, dans laquelle l'alcool, acceptable d'un point de vue pharmaceutique, est un mélange d'éthanol et d'alcool benzylique.

26. Préparation pharmaceutique selon la revendication 25, dans laquelle l'éthanol et l'alcool benzylique sont présents avec des % en poids environ égaux par volume de préparation.

27. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 26, dans laquelle le volume total de la préparation est de 6 ml ou moins et la concentration en fulvestrant est de 45 $mg.ml^{-1}$ au moins.

28. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 27, dans laquelle la quantité totale de fulvestrant dans la préparation est de 250 mg ou plus et le volume total de la préparation est de 6 ml ou moins.

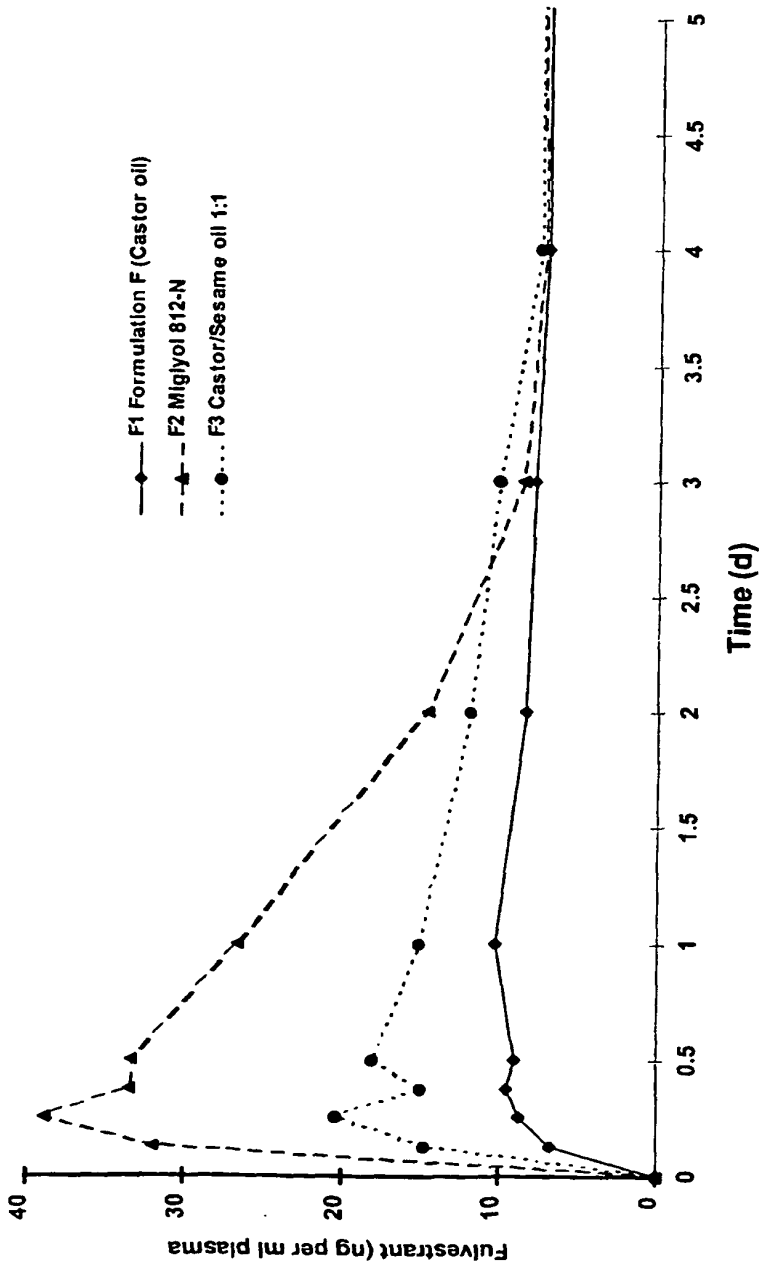
29. Préparation pharmaceutique selon la revendication 28, dans laquelle la quantité totale de fulvestrant dans la préparation est de 250 mg et le volume total de la préparation est de 5 à 5,25 ml.

30. Préparation pharmaceutique selon l'une quelconque des revendications 1 à 29, dans laquelle l'alcool, acceptable d'un point de vue pharmaceutique, est un mélange de 10% en poids d'éthanol par volume de préparation, de 10% en poids d'alcool benzylique par volume de préparation, la préparation contient 15% en poids de benzoate de benzyle par volume de préparation et le véhicule de ricinoléate est de l'huile de castor.

31. Préparation pharmaceutique adaptée à une injection intramusculaire, selon l'une quelconque des revendications 1 à 30, à utiliser dans une thérapie médicale.

32. Utilisation de fulvestrant dans l'élaboration d'une préparation pharmaceutique, selon l'une quelconque des revendications 1 à 30, destinée au traitement d'une maladie bénigne ou maligne du sein ou de l'appareil reproducteur.

33. Seringue ou flacon contenant une préparation pharmaceutique, selon la revendication 30.



INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) PTO Form 1449 June 4, 2009	Attorney Docket No. **056291-5004-02**	Application No. **12/285,887**
	Applicants: **John R. EVANS *et al.***	
	Filing Date: **October 15, 2008**	Group Art Unit: **1617**

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(71) Applicants *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MERIAL LLC [US/US]; 2100 Ronson Road, ISD – 200F, Iselin, NJ 08830–3077 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: WILLIAMS, James, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CHERN, Rey, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: LONG ACTING INJECTABLE FORMULATIONS CONTAINING HYDROGENATED CASTOR OIL

(57) Abstract

This invention relates to novel, long–acting injectable formulations. These formulations comprise: (a) a therapeutic agent selected from the group consisting of, e.g., insecticides, acaricides, parasiticides, growth enhancers and oil–soluble NASIDS; (b) hydrogenated castor oil and (c) a hydrophobic carrier comprising: (i) triacetin, benzyl benzoate or ethyl oleate or a combination thereof; and (ii) acylated monoglycerides, propyl dicaprylates/dicaprates or caprylic/capric acid triglycerides or a combination thereof. Also provided herein is a method for the treatment or prevention of various disease states by the parental administration of the invention formulations.

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TITLE OF THE INVENTION
LONG ACTING INJECTABLE FORMULATIONS CONTAINING HYDROGENATED CASTOR OIL

CROSS REFERENCE TO RELATED APPLICATIONS

Reference is made to provisional U.S. application Serial No. 60/067,374, filed on December 3, 1997. That application, as well as all documents cited herein and all documents cited in documents cited herein, are hereby incorporated by reference.

SUMMARY OF THE INVENTION

This invention is concerned with the unexpectedly long duration of activity which is observed when injectable formulations containing certain therapeutic agents are prepared using hydrogenated castor oil and a combination of hydrophobic or water immiscible carriers. Thus, it is an object of this invention to provide such a prolonged therapeutic effect. An additional object is to describe the therapeutic agents which may be employed in the long acting formulations. A still further object is to provide additional components which may be employed in the formulations. Additional objects will become apparent from a reading of the following description.

BACKGROUND OF THE INVENTION

The therapeutic agents which are used in the inventive formulations are well known to the practitioner to which this invention pertains. Classes of therapeutic agents contemplated by the inventive formulations include insecticides, acaricides, parasiticides, growth enhancers, and oil-soluble, nonsteroidal anti-inflammatory drugs (NSAIDS). Specific classes of compounds which fall within these classes include, for example, avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridylmethyl derivatives, phenylpyrazoles, and COX-2 inhibitors.

The avermectin and milbemycin series of compounds are potent anthelmintic and antiparasitic agents against a wide range of internal and external parasites. The compounds which belong to this series are either natural products or are semi-synthetic derivatives thereof. The structure of these two series of compounds are closely related and they both share a complex 16-membered macrocyclic lactone ring; however, the milbemycins do not contain the disaccharide substitutent in the 13-position of the lactone ring. The natural product avermectins are disclosed in U.S. Patent 4,310,519 to Albers-Schonberg, *et al.*, and the 22, 23-dihydro avermectin compounds are disclosed in Chabala, *et al.*, U.S. Patent 4,199,569. For a general discussion of avermectins, which include a discussion of their uses in humans and animals, see "Ivermectin and Abamectin," W.C. Campbell, ed., Springer-Verlag, New York (1989). Naturally occurring milbemycins are described in Aoki *et al.*, U.S. Patent 3,950,360 as well as in the various references cited in "The Merck Index" 12th ed., S. Budavari, Ed., Merck & Co., Inc. Whitehouse Station, New Jersey (1996). Semisynthetic derivatives of these classes of compounds are well known in the art and are described, for example, in U.S. Patent 5,077,308, U.S. Patent 4,859,657, U.S. Patent 4,963,582, U.S. Patent 4,855,317, U.S. Patent 4,871,719, U.S. Patent 4,874,749, U.S. Patent 4,427,663, U.S. Patent 4,310,519, U.S. Patent 4,199,569, U.S. Patent 5,055,596, U.S. Patent 4,973,711, U.S. Patent 4,978,677, and U.S. Patent 4,920,148.

European Patent Application 413,538 relates to an injectable formulation containing an avermectin compound and triacetin. European Patent Application 535,734 relates to an injectable formulation containing an avermectin compound and hydrogenated castor oil in a hydrophobic carrier such as triacetin. The formulations in both European Patent Applications are said to provide efficacy against external and internal parasites in animals only for up to 42 days. Neither of these applications suggests or teaches how to manipulate the composition of the formulation in order to achieve efficacy beyond 42 days.

Nodulisporic acid and its derivatives are a class of acaricidal, antiparasitic, insecticidal and anthelminitic agents known to a practitioner of the art. These compounds are used to treat or prevent infections in humans and animals. These compounds are described, for example, in U.S. Patent 5,399,582 and WO 96/29073. Additionally, the compounds can be administered in combination with other insecticides, parasiticides, and acaricides. Such combinations include anthelminitic agents, such as those discussed above which include ivermectin, avermectin, and emamectin, as well as other agents such as thiabendazole, febantel or morantel; phenylpyrazoles such as fipronil; and insect growth regulators such as lufenuron. Such combinations are also contemplated in the present invention.

Generally, all classes of insecticides are provided for in this invention. One example of this class include substituted pyridylmethyl derivatives such as imidacloprid. Agents of this class are described, for example, in U.S. Patent 4,742,060 or in EP 892,060. It would be well within the skill level of the practitioner to decide which individual compound can be used in the inventive formulation to treat a particular infection of an insect.

Phenylpyrazoles are another class of insecticides which possess excellent insecticidal activity against all insect pests including blood-sucking pests such as ticks, fleas etc., which are parasites on animals. This class of agents kills insects by acting on the gamma-butyric acid receptor of invertebrates. Such agents are described, for example, in U.S. Patent No. 5,567,429, U.S. Patent No. 5,122,530, and EP 295,117. It would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulations.

Insect growth regulators are another class of insecticides or acaricides, which are also provided for in the inventive formulations. Compounds belonging to this group are well known to the practitioner and represent a wide range of different chemical classes. These compounds all act by interfering with the development or growth of the

insect pests. Insect growth regulators are described, for example, in U.S. Patent 3,748,356; U.S. patent 3,818,047; U.S. Patent 4,225,598; U.S. Patent 4,798,837; and U.S. Patent 4,751,225, as well as in EP 179,022 or U.K. 2,140,010. Again, it would be well within the skill level of the practitioner to decide which individual compounds can be used in the inventive formulation.

Estrogens, progestins, and androgens refers to classes of chemical compounds which are also well known to a practitioner in this art. In fact, estrogens and progestins are among the most widely prescribed drugs and are used, for example, alone or in combination for contraception or hormone replacement therapy in post menopausal women. Estrogens and progestins occur naturally or are prepared synthetically. This class of compounds also includes estrogens or progesterone receptor antagonists. Antiestrogens, such as tamoxifen and clomiphene, are used to treat breast cancer and infertility. Antiprogestives are used as contraceptives and anticancer drugs, as well as to induce labor or terminate a pregnancy.

The androgens and antiandrogens structurally related to the estrogens and progestins as they are also biosynthesized from cholesterol. These compounds are based on testosterone. Androgens are used for hypogonadism and promote muscle development. Antiandrogens are used, for example, in the management of hyperplasia and carcinoma of the prostate, acne, and male pattern baldness as well as in the inhibition of the sex drive in men who are sex offenders. Estrogen, progestins, and androgens are described, for example, in "Goodman & Gilman's The Pharmacological Basis of Therapeutics," 9th ed., J.G. Handman and L. Elimbird, eds., Ch. 57 to 60, pp. 1411-1485, McGraw Hill, New York (1996) or in "Principles of Medicinal Chemistry," 2nd ed., W.O. Foye, ed., Ch. 21, pp. 495-559, Lea & Febiger, Philadelphia (1981).

Estrogens, progestins and androgens are also used in animal husbandry as growth promoters for food animals. It is known in the art that compounds of these classes act as growth-promoting steroids

in animals such as cattle, sheep, pigs, fowl, rabbits, etc. Delivery systems to promote the growth of animals are described, for example, in U.S. Patent 5,401,507, U.S. Patent 5,288,469, U.S. Patent 4,758,435, U.S. Patent 4,686,092, U.S. Patent 5,072,716 and U.S. Patent 5,419,910.

NSAIDS are well known in the art. The classes of compounds which belong to this group include salicylic acid derivatives, para-aminophenol derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids (fenamates), enolic acids, and alkanones. NSAIDS exert their activity by interfering with prostaglandin biosynthesis by irreversibly or reversibly inhibiting cycloxygenase. Also included are COX-2 inhibitors which act by inhibiting the COX-2 receptor. Compounds of this group possess analgesic, antipyretic and nonsteroidal anti-inflammatory properties. Compounds belonging to these classes are described, for example, in Chapter 27 of Goodman and Gilman on pages 617 to 658 or in Ch. 22 of Foye on pages 561 to 590 as well as in U.S. Patents 3,896,145; U.S. Patent 3,337,570; U.S. Patent 3,904,682; U.S. Patent 4,009,197; U.S. Patent 4,223,299; and U.S. Patent 2,562,830, as well as the specific agents listed in The Merck Index. This invention contemplates those compounds that are oil-soluble.

These and other embodiments are disclosed or are obvious from and encompassed by the following Detailed Description of the Invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a long acting injectable formulation for use in human and veterinary medicine, depending on the selected specific therapeutic agent and the indication being treated. The inventive formulation comprises:

(a) a therapeutic agent selected from the group consisting of , e.g., insecticides, acaricides, parasiticides, growth enhancers, and oil-soluble NSAIDS,

(b) hydrogenated castor oil, and

(c) a hydrophobic carrier comprising:

(i) triacetin, benzyl benzoate, or ethyl oleate or a combination thereof,

(ii) acylated monoglycerides, propyl dicaprylates/dicaprates and caprylic acid/capric triglycerides.

More preferred, are long-acting injectable formulations wherein

(a) a therapeutic agent selected from the group consisting of, e.g., avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, phenylpyrazoles and COX-2 inhibitors,

(b) hydrogenated castor oil, and

(c) a hydrophobic carrier comprising:

(i) triacetin, benzyl benzoate, or ethyl oleate or a combination thereof,

(ii) acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric acid triglycerides or a combination thereof.

The formulations of the present invention considerably prolong the duration of activity. By the term "acyl" Applicants mean an organic acid group in which the OH of the carboxyl group is replaced by some other substituent; i.e., RCO wherein R is, for example a C_1-C_{10}-alkyl group or a carbocyclic aromatic or a heteroaromatic group. Examples of such groups include acetyl, propionyl, butyryl, isobutyryl, and benzoyl. The term "prolonged duration of activity" means that the activity of the therapeutic agent is extended beyond the time period normally achieved when the therapeutic agent is injected into a host using a conventional, prior art carrier. As conventional injectable formulations are well known in the art, a skilled practitioner could readily understand the meaning of this term. Generally, depending upon the agent, host, and disease state, activity can be prolonged for a period from up to 120 days to up to 180 days. Preferable time periods in which the duration of the agent is prolonged includes from 14 days to 180

days, 30 days to 150 days, 42 days to 120 days, and 60 days to 90 days. While not wishing to be bound by theory, it is believed this increase in activity is achieved because the inventive formulations significantly increase the plasma concentration in tissue for an extended period of time by up to about 2 weeks to about 24 weeks, with time periods of up to about 6, 8, 10, 12, 16 and 20 weeks being observed. With respect to avermectins and milbemycins, the present formulations have been found to have a considerably prolonged duration against internal and external parasites over prior injectable formulation of avermectins or milbemycins. In addition, the present formulations for avermectin and milbemycin provide significantly higher plasma levels at day 42 than prior long-acting formulations thereby producing efficacy for all relevant parasitic species.

Preferred long-acting injectable formulations comprise:

(a) about 1.0 to about 10.0% w/v of a therapeutic agent,

(b) about 1 to about 3% w/v of hydrogenated castor oil, and

(c) a hydrophobic carrier comprising:

(i) about 30 to about 45% v/v of triacetin; benzyl benzoate or ethyl oleate; and

(ii) about 55 to 70% of v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

Even more preferred are the above formulations wherein about 1.0 to about 5.0% w/v of a therapeutic agent is present. Especially preferred are the inventive formulations wherein about 2.5 to about 5.0% w/v of a therapeutic agent is present.

Especially preferred long-acting formulation of the present invention comprises:

(a) an avermectin or milbemycin compound,

(b) hydrogenated castor oil, and

(c) triacetin and acetylated monoglycerides.

In an especially preferred embodiment, the long-acting formulation comprises:

(a) about 1.0 to about 5.0% w/v of an avermectin or milbemycin compound,

(b) about 0.5 to about 3.5% w/v of hydrogenated castor oil, and

(c) about 30 to about 45% v/v of triacetin and about 55 to about 70% v/v of acetylated monoglycerides.

In a most preferred embodiment, the long-acting formulation comprises:

(a) 3.15% w/v of ivermectin,

(b) 1% w/v of hydrogenated castor oil, and

(c) 40% v/v of triacetin and up to 60% v/v of acetylated monoglycerides.

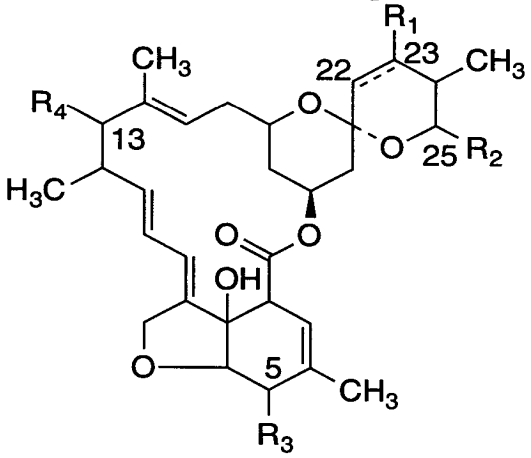
Another aspect of the invention is to provide a method for the prevention or treatment of parasite or insect infestations in a host in need thereof for an extended period of time by administering a single dose of a long-acting injectable formulation comprising the appropriate therapeutic agent. That duration typically, for example, lasts from up to about 1 month to about six months, depending upon the agent, host and indication being treated. Extensions of activity lasts from up to about 2 months to about 5 months and especially from up to 3 months to up to 4 months are observed. A further aspect of this invention is to promote the growth in animals by administering a single long-acting formulation according to the present invention wherein the therapeutic agent is an estrogen, progestin, or androgen. Another aspect of the present invention is a method to treat inflammation, pain or fever for an extended period of time in a host in need thereof by administering a single-dose of a formulation according to the present invention wherein the therapeutic agents are oil-soluble NSAIDS. An especially preferred aspect of the invention is to provide a method for the prevention or treatment of parasitic infestation in cattle for a minimum of 42 days which comprises administering to said cattle a single dose of a long-

acting injectable formulation according to the present invention where the therapeutic agent is an avermectin or milbemycin.

Therapeutic agents used in the invention formulations include all known avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, oil-soluble NSAIDS, phenylpyrazoles, substituted pyridylmethyl compounds, and agents which act as insect growth regulators, which are compatible in the inventive formulations for their intended use. The ester and amide derivatives of these compounds, where applicable, as well as their salt forms are also contemplated. Specific compounds which belong to these classes of therapeutic agents are well known to the practitioner of this art. Likewise, the specific disease state as well as the particular dose would be well known to the practitioner.

Avermectins and milbemycins share the same common 16-membered macrocyclic lactone ring; however milbemycins do not possess the disaccharide substituent on the 13-position of the lactone ring.

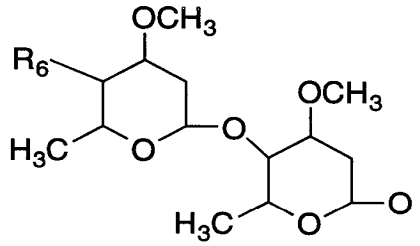
While many avermectin compounds are known in the art, a representative structure of the class of compounds is as follows:



where the broken line indicates a single or a double bond at the 22,23-positions;

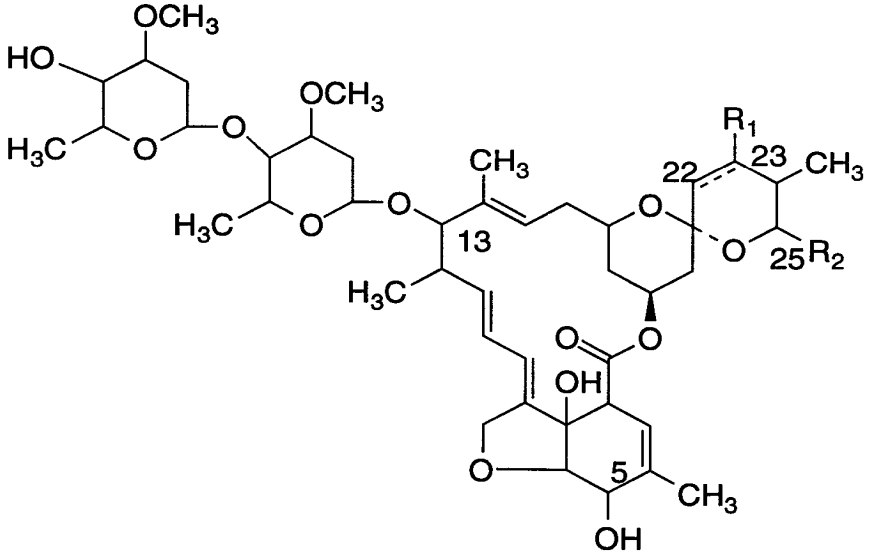
R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;
R_3 is hydroxy, methoxy or = NOR_5 where R_5 is hydrogen or lower alkyl; and
R_4 is hydrogen, hydroxy or



where R_6 is hydroxy, amino, mono-or di-lower alkylamino or lower alkanoylamino.

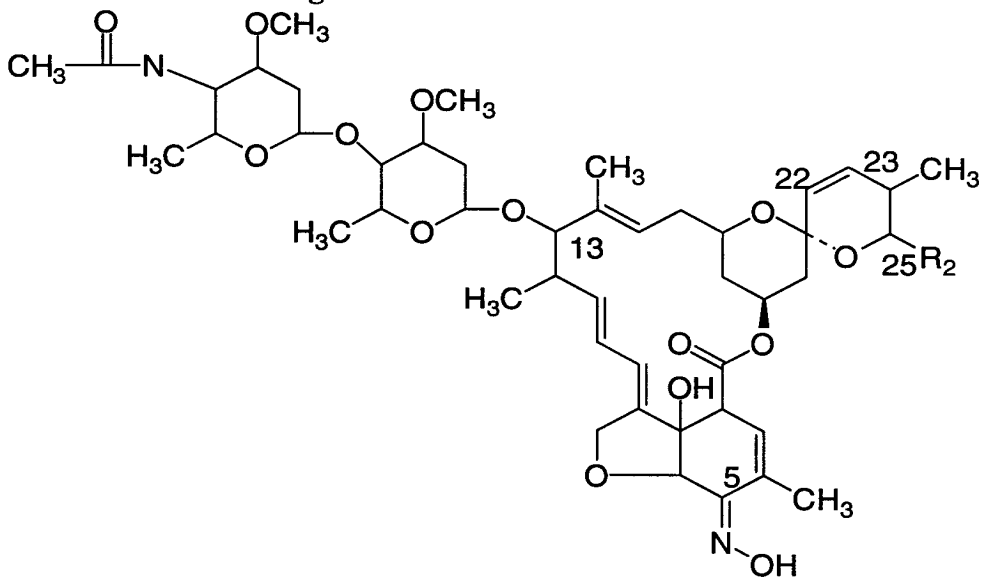
The preferred compounds are avermectin Bla/Blb (abamectin), 22,23-dihydro avermectin Bla/Blb (ivermectin) and the 4"-acetylamino-5-ketoximino derivative of avermectin Bla/Blb. Both abamectin and ivermectin are approved as broad spectrum antiparasitic agents. The structures of abamectin and ivermectin are as follows:



wherein for abamectin the broken line represents a double bond and R_1 is not present and for ivermectin the double bond represents a single bond and R_1 is hydrogen; and

R_2 is isopropyl or sec-butyl.

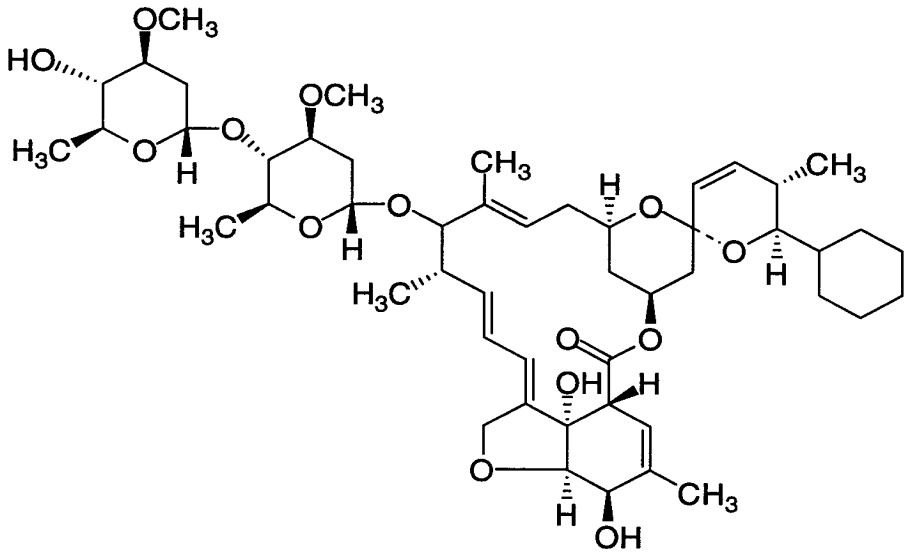
The 4"-acetylamino-5-ketoximino derivatives of avermectin Bla/Blb has the following structural formula:



where R_2 is isopropyl or sec-butyl.

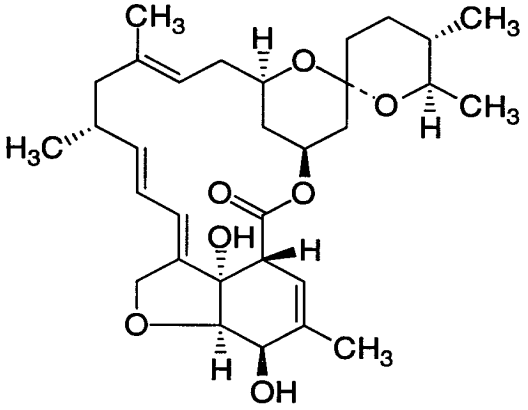
The avermectin products are generally prepared as a mixture of at least 80% of the compound where R_2 is sec-butyl and no more than 20% of the compound where R_2 is isopropyl.

Other preferred avermectins, include ememectin, epinomectin and doramectin. Doramectin is disclosed in U.S. Patent 5,089,490 and EP 214738. This compound has the following structure:

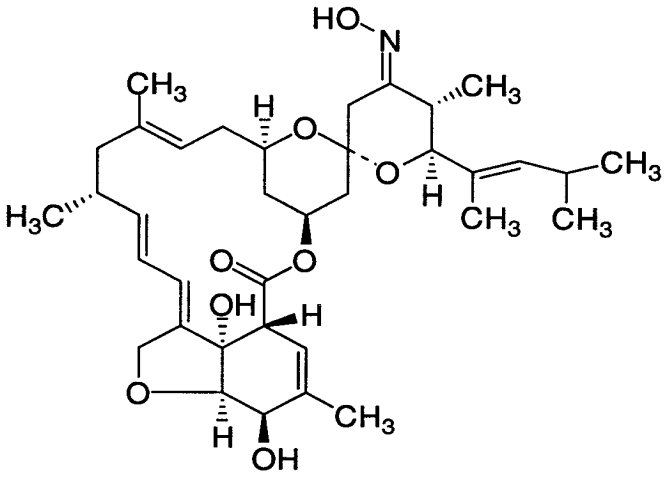


In the present formulations, ivermectin is especially preferred.

A representative structure for a milbemycin is that for milbemycin α_1:



An especially preferred milbemycin is moxidectin, whose structure is as follows:



The compound is disclosed in U.S. Patent No. 5,089,490.

Insecticides contemplated by this invention are also well known in the art and such compounds include substituted pyridylmethyl derivatives and phenylpyrazoles. An especially preferred substituted pyridylmethyl derivative is imidacloprid. An especially preferred phenylpyrazole is fipronil, whose chemical name is 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylpyrazole. Fipronil is well known in the art as a flea and tick agent. Additional insecticides included by the invention include insect growth regulators. Especially preferred insect growth regulators include diflubenzuron, lufenuron, methoprene, phenoxycarb, pyriproxyfen, and cyromazine.

Specific estrogen, progestin and androgen compounds are well known to the practitioner. Especially preferred compounds belonging to this class include progesterone, estradiol benzoate and trenbolone acetate.

Oil-soluble NSAIDS are also well known to the practitioner. Classes of NSAIDS which are preferred are indole and indecene acetic acids and heteroaryl acetic acids. Especially preferred compounds include indomethacin, ketorolac, caprofen, flunixin, ketoprofen, meloxicam, naproxen, and phenylbutazone.

Hydrogenated castor oil is refined, hydrogenated, and deodorized castor oil, consisting mainly of the triglyceride of

hydroxystearic acid. The hydrogenated castor oil is readily prepared using normal techniques known to those skilled in the art of preparing hydrogenated castor oils and one suitable form of hydrogenated castor oil is available commercially under the trade name "Thixcin R" from NL Industries. While not wishing to be bound by theory, it appears that hydrogenated castor oil, being a waxy hydrophobic solid, is left at the injection site entrapping the therapeutic agent after the hydrophobic carrier has diffused from the injection site; it is this hydrophobic hydrogenated castor oil/therapeutic agent matrix that forms a "depot" of the active material which slowly diffuses from the injection site over a prolonged period of time. The hydrogenated castor oil constitutes approximately 1% w/v of the present formulation.

The hydrophobic carrier of the present formulation comprises a mixture of

(i) triacetin, benzylbenzoate, ethyl oleate or a combination thereof; and

(ii) acylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides or a combination thereof.

These compounds as well as their sources are well known in the art. For example, triacetin (glyceryl triacetate or glycerol triacetate) and acetylated monoglycerides (available under the tradename "Myvacet 9-45" from Quest International). The ratio of component (i) to component (ii) used in the present formulation is generally from 45:55 to 30:70; preferably the ratio is approximately 40:60. In addition to the hydrogenated castor oil, the therapeutic agent and the hydrophobic carrier, the formulation can contain other inert ingredients such as antioxidants or preservatives. Antioxidant such as a propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like may be added to the present formulation. The antioxidants are generally added to the formulation in amounts of from about 0.01 to about 2.0% (w/v). Preservatives such as

the parabens (methylparaben and/or propylparaben) are suitably used in the formulation in amounts ranging from about 0.01 to about 2.0 w/v.

The long-acting injectable formulation of the present invention may be prepared by adding a dispersion of hydrogenated castor oil in acetylated monoglycerides, propyl dicaprylates/dicaprates or caprylic/capric triglycerides to a solution comprising the therapeutic agent, and any other inert ingredients, in triacetin benzyl benzoate or ethyl oleate, and mixing the liquids until uniform. Since the long acting formulation is intended for injection, it is necessary that it be sterilized. Heat sterilization is generally to be avoided in the situation where avermectin or milbemycin compounds are used since these compounds are unstable at autoclave temperatures. Rather, membrane sterilization is preferred in those situations with dissolved solids and gamma sterilization for the hydrogenated castor oil. The sterile hydrogenated castor oil is dispersed in the product aseptically and then aseptically packaged.

The instant formulation is equally applicable to other compounds used for injection as long as such compounds are soluble in the mixture of the hydrogenated castor oil and hydrophobic carrier. Additional compounds that can be used in this formulation are other antiparasitic agents and antibiotics, therapeutic vitamin and mineral supplements, and other agents that are assisted in their therapeutic effect by having their effects extended over a prolonged period of time. Again, such compounds would be well known to the practitioner.

The instant long-acting formulations are administered to a warm-blooded animals such as humans, cattle, sheep, pigs, cats, dogs, horses, and the like by intramuscular or subcutaneous injection. The amount of therapeutic agent depends on the individual therapeutic agent, the animal being treated, the disease state, and the severity of the disease state. The determination of those factors is well within the skill level of the practitioner. Generally, such preparation normally contain about 0.0005 to about 50% w/v of therapeutic agent. Preferred formulations are those containing about 0.01 to 10% w/v of therapeutic

agent and especially preferred formulations are those containing about 2.5 to about 5% w/v of therapeutic agent. For the avermectins and milbemycins, the formulations will generally be prepared to administer from about 0.1 to about 2 mg/kg, preferably from about 0.4 to about 0.85 mg/kg and most preferably from about 0.6 to about 0.7 mg/kg of the active ingredient. At a preferred dose volume of about 1 ml to treat 50 kg of animal body weight the formulation contains from about 5 to about 50 mg of the active agent per ml of solution or about 0.5 to about 10%, w/v preferably about 2.5 to about 5% w/v. However, depending upon the activity of the compound and the animal being treated, doses as low as about 0.3% w/v of the active ingredient are usable. For nodulisporic acid and its derivatives, a formulation containing about 0.0005 to about 5% w/v of the active compound is preferred.

The present formulation provides for an extended period of treatment. For avermectins and milbemycins a minimum of 42 days of activity against endo- and ectoparasites is obtained without causing tissue irritation. The extended period of time for the other therapeutic agents is readily determined by one skilled in the art and is determined by such factors as the therapeutic agent, disease state, host and severity of the infection. While the previously reported avermectin formulation containing hydrogenated castor oil in triacetin did produce prolonged plasma level compared to a formulation without hydrogenated castor oil, it did not achieve a plasma level efficacious against all relevant parasitic species at the 42 day target. In contrast the present formulation using avermectins or milbemycins surprisingly provides a significantly higher plasma at day 42 and beyond. The present formulation is also efficacious against ticks and Dermatobia hominis for up to 75 and 140 days, respectively.

The following example is provided in order that the invention might be more fully understood. It is not to be construed as a limitation of the invention.

EXAMPLE 1

Material	%	Amount
Ivermectin	3.15% w/w	17.6 gm
n-propyl gallate	0.02% w/w	0.10 gm
Thixcin R	1.0% w/w	5.0 gm
triacetin	40.0% w/w	200.0 gm
Myvacet 9-45	qs 100% w/w	qs to 500.0 gm

Triacetin was added to n-propyl gallate and ivermectin in an Erlenmyer flask and mixed until all of the n-propyl gallate dissolved. Myvacet 9-45 was placed in a non-glass beaker in a 50°C water bath, and mixed at a low speed with a dispersator mixer until the temperature of the content reached 50°C. Thixcin R was then added slowly to the vortex of the mixing Myvacet 9-45. When all the Thixcin R was added, the speed of the mixer was slowly increased to 60 rpm and mixing continued for 20 minutes. The beaker was removed from the water bath and allowed to cool to 30°C, while mixing continued at about 25 rpm. The triacetin solution was added to the Thixcin R/Myvacet 9-45 mixture and the liquids were mixed until uniform.

EXAMPLE 2

Material	%	Amount/2000 L.
Ivermectin	3.15% w/w	63.0 kg
triacetin	40.0% v/v	800.0 L
hydrogenated castor oil	1.0% w/w	20.0 kg
BHT	0.02 w/v	0.4 kg
methylparaben	0.18% w/v	3.6 kg
propylparaben	0.02% w/v	0.4 kg
Myvacet 9-45	qs 100% v/v	qs to 1200.0 L

Ivermectin, BHT, methyl and propyl paraben were dissolved in 800 L of triacetin, and the solution was sterile filtered into a 2000 L tank equipped with an agitator. Myvacet 9-45 was sterile filtered into a 150 L tank capable of maintaining a batch temperature of 60°C and

equipped with an agitator and with an aseptic addition of sterile powder capability. The gamma sterilized hydrogenated castor oil was dispersed in the Myvacet 9-45, and the dispersion was heated to 50°C, then transferred to the triacetin solution through a microfluidizer. The liquids were mixed until uniform and then aseptically packaged in low density polyethylene containers.

EXAMPLE 3

The plasma levels of ivermectin administered once subcutaneously at a dose of 630 mcg/kg bodyweight were determined in cattle for two formulations: formulation I contains ivermectin 3.15%, n-propyl gallate 0.02%, Thixcin R 1.5% and triacetin qs to 100%; formulation II has the composition given in Example 2. Ten animals were used for formulation I and six were used for formulation II. Mean plasma levels (ng/ml) are shown in the following Table:

	Days post dosing					
Formulation	3	14	21	28	35	42
I	80	18	10	6	4	2
II	21	25	22	16	13	9

The mean plasma level for formulation II was greater than 3 ng/ml on day 70.

The 42-day plasma level of formulation I (2 ng/ml) is not sufficient to produce efficacy against Cooperia onocophora and Nematodirus which require an ivermectin plasma level of 3 to 4 ng/ml.

EXAMPLE 4

To facilitate the manufacture of large scale batches the following process was developed which results in a product that meets

the same release specifications as the product manufactured in Example 2. The formula is also the same as used in Example 2. Ivermectin, BHT, methyl and propyl paraben are dissolved a mixture of the triacetin and Myvacet 9-45. The solution is sterile filtered. The gamma sterilized hydrogenated castor is aseptically dispersed in sterile solution using an in-line educator/homogenizer system. Such in-line system can be a Flashblend system. The product is heated and recirculated through the system until the product temperature is from 42 to 50°C. Then the product is aseptically packaged.

* * *

Having thus described in detail preferred embodiments of the present invention, it is to be understood that the invention defined by the appended claims is not to be limited by particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope thereof.

WHAT IS CLAIMED IS:

1. A long-acting injectable formulation comprising:

(a) a therapeutic agent selected from the group consisting of insecticides, acaricides, parasiticides, growth enhancers and oil-soluble NASIDS,

(b) hydrogenated castor oil, and

(c) a hydrophobic carrier comprising:

(i) triacetin, benzyl benzoate or ethyl oleate or a combination thereof; and

(ii) acylated monoglycerides, propyl dicaprylates/dicaprates, caprylic/capric acid triglycerides, or a combination thereof.

2. A long-acting injectable formulation comprising:

(a) a therapeutic agent selected from the group consisting of avermectins, milbemycins, nodulisporic acid and its derivatives, estrogens, progestins, androgens, substituted pyridylmethyl derivatives, phenylpyrazoles, and COX-2 inhibitors,

(b) hydrogenated castor oil, and

(c) a hydrophobic carrier comprising:

(i) triacetin, benzyl benzoate or ethyl oleate or a combination thereof; and

(ii) acetylated monoglycerides, propyl dicaprylates/dicaprates, caprylic/capric triglycerides, or a combination thereof.

3. The long-acting injectable formulation according to claim 1 comprising

(a) about 1.0 to about 10.0 w/v of a therapeutic agent;

(b) about 0.3 to about 5% w/v of hydrogenated castor oil;

(c) a hydrophobic carrier comprising:

(i) about 30 to about 45% v/v of triacetin; benzylbenzoate or ethyloleate; and

(ii) about 55 to 70% of v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

4. The long-acting injectable formulation according to claim 2 comprising

(a) about 1.0 to about 10.0 w/v of a therapeutic agent;

(b) about 0.3 to about 5% w/v of hydrogenated castor oil;

(c) a hydrophobic carrier comprising:

(i) about 30 to about 45% v/v of triacetin; benzyl benzoate or ethyl oleate; and

(ii) about 55 to 70% of v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

5. The long-acting injectable formulation according to claim 2 wherein about 2.5 to about 5.0% w/v of a therapeutic agent is present.

6. The long-acting injectable formulation according to claim 2 wherein the therapeutic agent is an avermectin or a milbemycin.

7. The long-acting injectable formulation according to claim 6, wherein the avermectin is ivermectin, abamectin, ememectin, eprinomectin, or doramectin and the milbemycin is moxidectin.

8. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is an estrogen, progestin or androgen.

9. The long-acting injectable formulation according to claim 8, where the estrogen, progestin or androgen is estradiol benzoate, progesterone, or trenbolone acetate.

10. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is nodulisporic acid or its derivatives.

11. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is a substituted pyridylmethyl derivative or a phenylpyrazole.

12. The long-acting injectable formulation according to claim 11, wherein the therapeutic agent is imidacloprid or fipronil.

13. The long-acting injectable formulation according to claim 2, wherein the therapeutic agent is a COX-2 inhibitor.

14. The long-acting injectable formulation according to claim 1, wherein the therapeutic agent is an oil-soluble, nonsteroidal anti-inflammatory drug.

15. The long-acting injectable formulation according to claim 14, wherein the therapeutic agent is carprofen, flunixin, ketoprofen, meloxicam, naproxen or phenylbutazone.

16. The long-acting injectable formulation according to claim 1, wherein the therapeutic agent is an insect growth regulator.

17. The long-acting injectable formulation according to claim 16, wherein the therapeutic agent is diflubenzuron, lufenuron, methoprene, phenoxycarb, pyriproxyfen, and cyromazine.

18. The long-acting injectable formulation according to claim 1, which further comprises an antioxidant or a preservative.

19. The long-acting injectable formulation according to claim 2 where about 1 to about 3.0 % w/v of hydrogenated caster oil is present and hydrophobic carrier comprises about 40% v/v of triacetin, benzlybenzoate or ethyloleate and about 60% v/v of acetylated monoglycerides, propyl dicaprylates/dicaprates, or caprylic/capric triglycerides.

20. The long-acting injectable formulation of claim 2 which comprises:

(a) about 1.0 to about 5.0% w/v of an avermectin compound,

(b) about 1 to about 3% w/v of hydrogenated castor oil, and

(c) about 30 to about 45% v/v of triacetin and 55 to 70% v/v of acetylated monoglycerides.

21. The long-acting injectable formulation of claim 2 which comprises:

(a) about 3.15% w/v of ivermectin,

(b) about 1% w/v of hydrogenated castor oil, and

(c) about 40% of triacetin and up to about 60% v/v of acetylated monoglycerides.

22. The long-acting injectable formulation of claim 2 which further comprises an antioxidant.

23. The long acting injectable formulation of claim 2 which further comprises a preservative.

24. The long acting injectable formulation of claim 22 wherein said antioxidant is selected from n-propyl gallate, BHA, BHT and monothioglycerol.

25. The long-acting injectable formulation of claim 23 wherein said preservative is selected from the parabens.

26. The long-acting injectable formulation of claim 21 which further comprises an antioxidant selected from n-propyl gallate, BHA, BHT and monothioglycerol.

27. The long-acting injectable formulation of claim 26 which further comprises a preservatives selected from the parabens.

28. The long acting injectable formulation of claim 21 which further comprises BHT and one or more preservatives from the parabens.

29. A method for the prevention or treatment of parasitic infestation in a host in need thereof, which comprises parentally administering a single dose of a long-acting injectable formulation of claim 6 to said host.

30. A method for the prevention or treatment of parasitic infestation in a host in need thereof for a minimum of 42 days which comprises administering to said host a single dose of a long-acting injectable formulation of claim 1.

31. A method for the prevention or treatment of parasitic infestation in cattle for a minimum of 42 days which comprises administering to said cattle a single dose of a long-acting injectable formulation of claim 2.

32. A method for the prevention or treatment of parasitic infestation in cattle for a minimum of 42 days which comprises administering to said cattle a single dose of a long-acting injectable formulation of claim 21.

33. A method for treating or preventing insect infestation for an extended period of time in a host in need thereof which comprises parentally administering a single-dose of a long-acting injectable formulation according to claim 10 to said host.

34. The method according to claim 33, wherein the insects are fleas.

35. A method for treating or preventing insect infestation for an extended period of time in a host in need thereof which comprises parenterally administering a single-dose of a long-acting injectable formulation according to claim 11 to said host.

36. The method according to claim 35 wherein the injectable formulation as the therapeutic agent is imidacloprid or fipronil and the insects are fleas.

37. A method for promoting growth in animals which comprises administering a single does of a long-acting injectable formulation according to claim 8 to said animal.

38. A method for treating inflammation, pain, or fever for an extended period of time in a host in need thereof which comprises administering a single-dose of a long-acting injectable formulation according to claim 14 to a host in need thereof.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 98/19016

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/08 A61K47/14 A61K47/44 A61K31/70 A61K31/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 11709 A (ASHMONT HOLDINGS LTD ;HARVEY COLIN MANSON (NZ)) 3 April 1997 see page 4 - page 5; examples 1-6 ---	1-38
A	EP 0 413 538 A (MERCK & CO INC) 20 February 1991 cited in the application see page 4 - page 5; example 1 ---	1-38
A	GB 1 060 632 A (OLIN MATHISON CHEMICAL CORP.) 8 March 1967 see page 3; example 2 ---	1-38
A	EP 0 535 734 A (MERCK & CO INC) 7 April 1993 cited in the application see page 4 - page 5; example 1 --- -/--	1-38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 1999	11/02/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Boulois, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/19016

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 29-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internr ıal Application No
PCT/US 98/19016

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DE 196 13 972 A (BAYER AG) 16 October 1997 see page 6 - page 10; examples 1-10	1-38
A	US 4 330 538 A (ITIL TURAN M ET AL) 18 May 1982 see column 3 - column 4; examples 2,4A	1-38
A	DE 25 48 413 A (SCHERING AG) 28 April 1977 see claim 3	1-38

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PATENT
Attorney Docket No. **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1199**
John R. EVANS *et al.*	)	
Application No.: **12/285,887**	)	Group Art Unit: **1617**
Filed: **October 15, 2008**	)	Examiner: **Unassigned**
FOR: **FORMULATION**	)	Date: **June 4, 2009**

SECOND INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

Applicants wish to specifically call to the Examiner's attention in this continuing application the same circumstances as detailed in the Second Information Disclosure Statements filed September 13, 2002 and October 18, 2004 in parent applications, a copy of this is attached hereto for convenience. Specifically, the attached Second Information Disclosure Statement details circumstances regarding the controlled, confidential and non-commercial testing of compositions falling within the scope of the definition of "pharmaceutical formulation", as used in the present method of treatment claims, which was carried out in the United States more than one year before the filing date of the parent application in preparation for and during the testing (IND) phase of the regulatory review of such formulation by the FDA.

The present Information Disclosure Statement is being filed before the mailing date of a first Office Action, and therefore no certification under 37 CFR §1.97(e) or fee under 37 CFR §1.17(p) is required.

This Information Disclosure Statement is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited, along with additional time under Rule 97(f), to enable Applicant to fully comply.

Consideration by the Examiner of the circumstances detailed in the attached document is respectfully requested when taking up this continuing application for a first Action on the merits.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby

authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **June 4, 2009**
Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000

By: /Donald Bird/
Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

DB1/63065165.1

FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation Application of copending U.S. Patent Application No. 10/872,784, filed June 22, 2004, which claims benefit of U.S. Patent Application No. 09/756,291, filed January 9, 2001 which claims the benefit of Great Britain Application No. 0008837.7 filed April 12, 2000 and Great Britain Application No. 0000313.7, filed January 10, 2000, all of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol~~, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle~~.

Description of the Related Art

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any

of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone

density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

SUMMARY OF THE INVENTION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 below, and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits.

DETAILED DESCRIPTION OF THE INVENTION

Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20
Miglyol 810	3.06

Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly

lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibly other organic solvents, for example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-

25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and difficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still achieved by the formulation of the invention.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v							
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100.	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols

	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site

	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+

0, +, ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

A further feature of the invention is a method of treating a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

Preferably 5ml of the intramuscular injection is administered.

A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably treating breast cancer.

Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary

pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram below

Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol

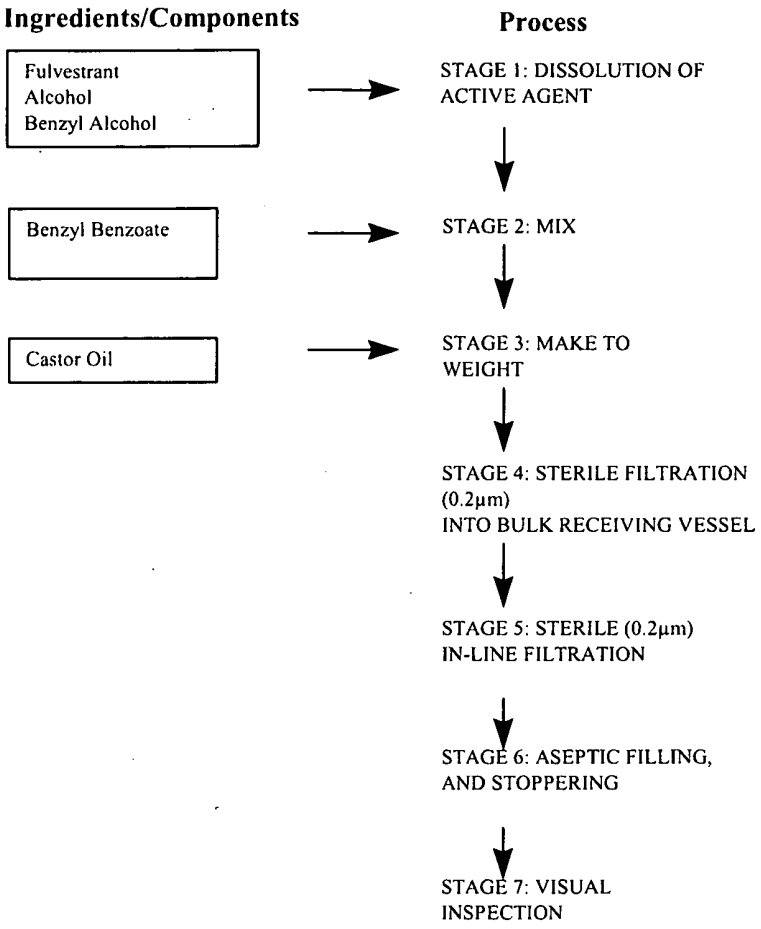
10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



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Claims

1. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration of at least $2.5ngml^{-1}$ for at least 2 weeks.

2. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for at least 4 weeks.

3. A pharmaceutical formulation as claimed in claim 1 wherein the blood plasma fulvestrant concentration is attained for 2 to 5 weeks.

4. A pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least $45mgml^{-1}$ of fulvestrant.

5. A pharmaceutical formulation as claimed in claim 1 to 4 which contains 25% w/v or less of a pharmaceutically-acceptable alcohol.

6. A pharmaceutical formulation as claimed in claim 5 which contains 20% w/v or less of a pharmaceutically-acceptable alcohol.

7. A pharmaceutical formulation as claimed in any claim from 1 to 6 which contains 60% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

8. A pharmaceutical formulation as claimed in claim 7 which contains 50%w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent .

9. A pharmaceutical formulation as claimed in claim 7 which contains 45% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

10. A pharmaceutical formulation as claimed in claim 7 which contains 40% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

11. A pharmaceutical formulation as claimed in claim 7 which contains 35% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

12. A pharmaceutical formulation as claimed in claim 7 which contains 30% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

13. A pharmaceutical formulation as claimed in claim 7 which contains 25% w/v or less of a pharmaceutically-acceptable non-aqueous ester solvent.

14. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the pharmaceutically-acceptable alcohol is a mixture of ethanol and benzyl alcohol.

15. A pharmaceutical formulation as claimed in any claim from 1 to 14 wherein the pharmaceutically-acceptable non-aqueous ester solvent is selected from benzyl benzoate, ethyl oleate, isopropyl myristate, isopropyl palmitate or a mixture of any thereof.

16. A pharmaceutical formulation as claimed in any claim from 1 to 15 wherein the pharmaceutically-acceptable non-aqueous ester solvent is benzyl benzoate.

17. A pharmaceutical formulation as claimed in any claim from 1 to 16 wherein the total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

18. A pharmaceutical formulation as claimed in any claim from 1 to 13 wherein the total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

19. A pharmaceutical formulation as claimed in claim 18 wherein the total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5 to 5.25ml.

20. A pharmaceutical formulation as claimed in any of claims 1-19 wherein the pharmaceutically-acceptable alcohol is a mixture of 10% weight of ethanol per volume of formulation, 10% weight of benzyl alcohol per volume of formulation and 15% weight of benzyl benzoate per volume of formulation and the ricinoleate vehicle is castor oil.

21. A method of treating a benign or malignant diseases of the breast or reproductive tract by administration to a human in need of such treatment by intramuscular a pharmaceutical formulation as claimed in claims 1 to 19.

22. A method as claimed in claim 21 for treating breast cancer.

23. A syringe or vial containing a pharmaceutical formulation as defined in claim 20.

~~ABSTRACT~~

~~TITLE: Formulation~~

ABSTRACT OF THE DISCLOSURE

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

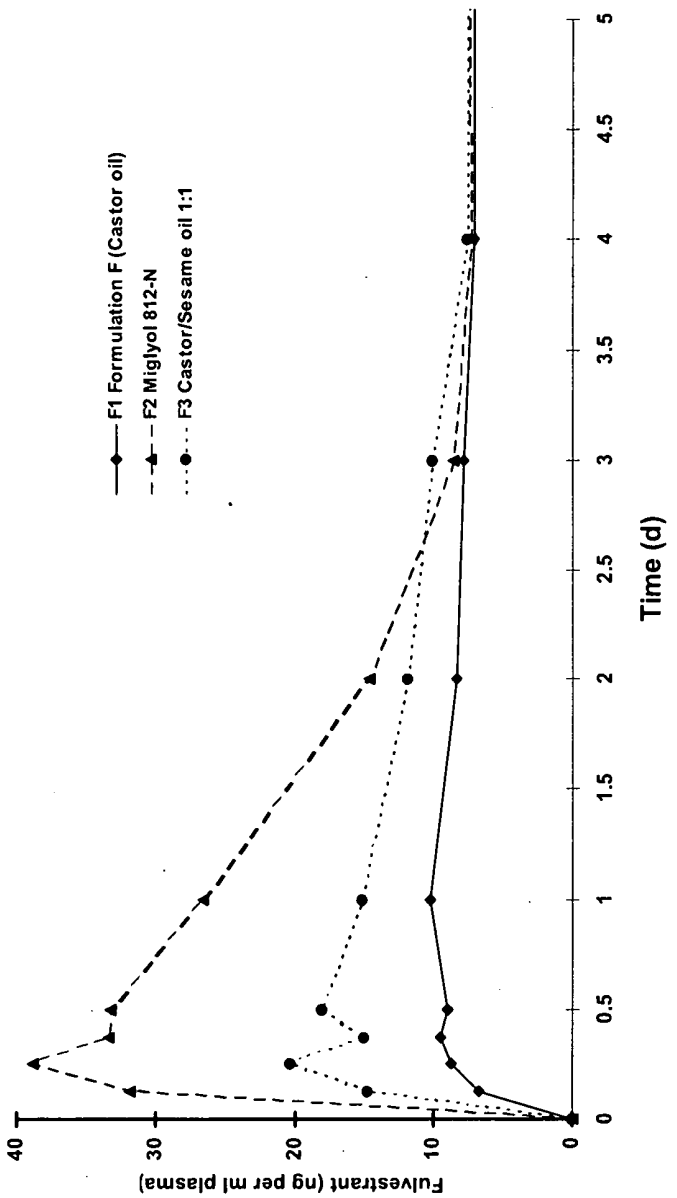
F1 Formulation F (Castor oil)
F2 Miglyol 812-N
F3 Castor/Sesame oil 1:1
Fulvestrant (ng per ml plasma)
0
10
20
30
40
Time (d)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

Figure 1

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/285,887	10/15/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/15/2008

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 23	Minus	** 23	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT 06/04/2009

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 23	Minus	** 23	= 0	X $ =		OR	X $52 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	X $ =		OR	X $220 =	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

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Legal Instrument Examiner:
/HELENA PAYTON/

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First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	09629
Filer:	Donald J. Bird
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WASHINGTON, DC 20004

Date Mailed: 06/17/2009

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Applicant(s)

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/872,784 06/22/2004 PAT 7,456,160

Foreign Applications

UNITED KINGDOM 0008837.7 04/12/2000
UNITED KINGDOM 0000313.7 01/10/2000

If Required, Foreign Filing License Granted: 11/03/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/285,887**

Projected Publication Date: 09/24/2009

Non-Publication Request: No

Early Publication Request: No

Title

Formulation

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	056291-5004-02

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

WITHDRAWAL NOTICE

OC000000037186366

Date Mailed: 08/03/2009

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 11/04/2008. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web. https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

/tnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	056291-5004-02

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

WITHDRAWAL NOTICE

OC000000037186358

Date Mailed: 08/03/2009

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 06/17/2009. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

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/tnguyen/

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/285,887	10/15/2008	1617	2754	056291-5004-02	23	2

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FILING RECEIPT

OC000000037186523

Date Mailed: 08/03/2009

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/285,887**

Projected Publication Date: None.

Non-Publication Request: No

Early Publication Request: No

Title

Formulation

Preliminary Class

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	056291-5004-02

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

FORMALITIES LETTER

OC000000037186524

Date Mailed: 08/03/2009

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The specification contains drawings or flow diagrams (37 CFR 1.58(a)) on page(s) 19. Drawings or flow diagrams cannot be embedded in the specification and should be submitted separately in accordance with 37 CFR 1.84. (Both a substitute specification in compliance with 37 CFR 1.125 and new drawings in compliance with 37 CFR 1.84 and 1.121(d) are required).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

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PATENT
Attorney Docket No. **056291-5004-02**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **1199**
John R. EVANS *et al.*	)	
Application No.: **12/285,887**	)	Group Art Unit: **1617**
Filed: **October 15, 2008**	)	Prior Examiner: **Unassigned**
FOR: **FORMULATION**	)	Date: **March 3, 2010**

STATEMENT ACCOMPANYING SUBSTITUTE SPECIFICATION

In response to the Notice to File Corrected Application Papers, attached are a clean copy and a marked up copy of the second substitute specification in which the flow diagram on page 19 has been removed and resubmitted as Figure 2. The attached copies of the substitute specification do not include prohibited new matter. In particular, referring to the "marked up" copy:

- At page 19, the flow diagram was deleted to create a new formal Figure 2.
- At page 6, "Brief Description" of the new Figure 2 was inserted.
- At page 18, the "below" reference was changed to refer to "Figure 2."
- Figure 1 was modified to designate "1/2" at the top

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: **March 3, 2010**
By: /Donald Bird/

Donald J. Bird
Registration No.25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000

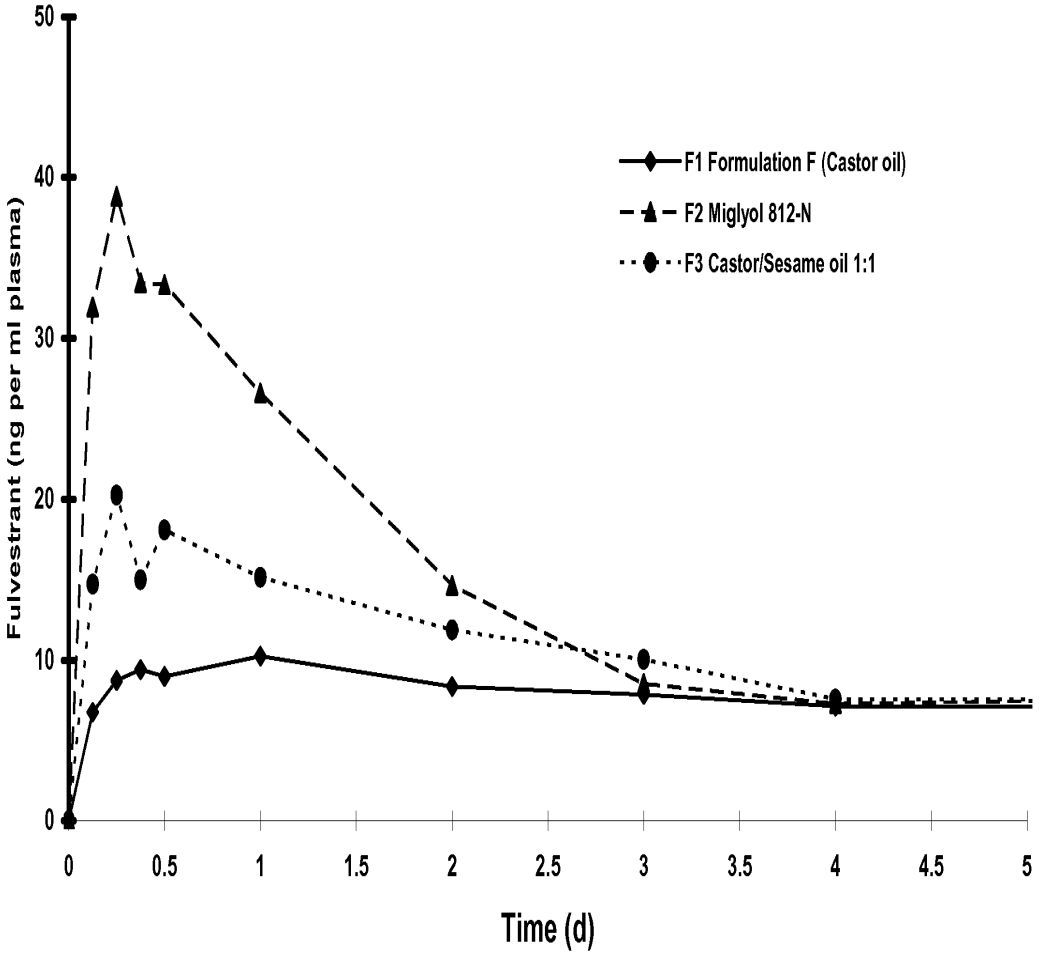
Fulvestrant (ng per ml plasma)
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Time (d)
F1 Formulation F (Castor oil)
F2 Miglyol 812-N
F3 Castor/Sesame oil 1:1

Figure 1

FLOW DIAGRAM OF MANUFACTURING

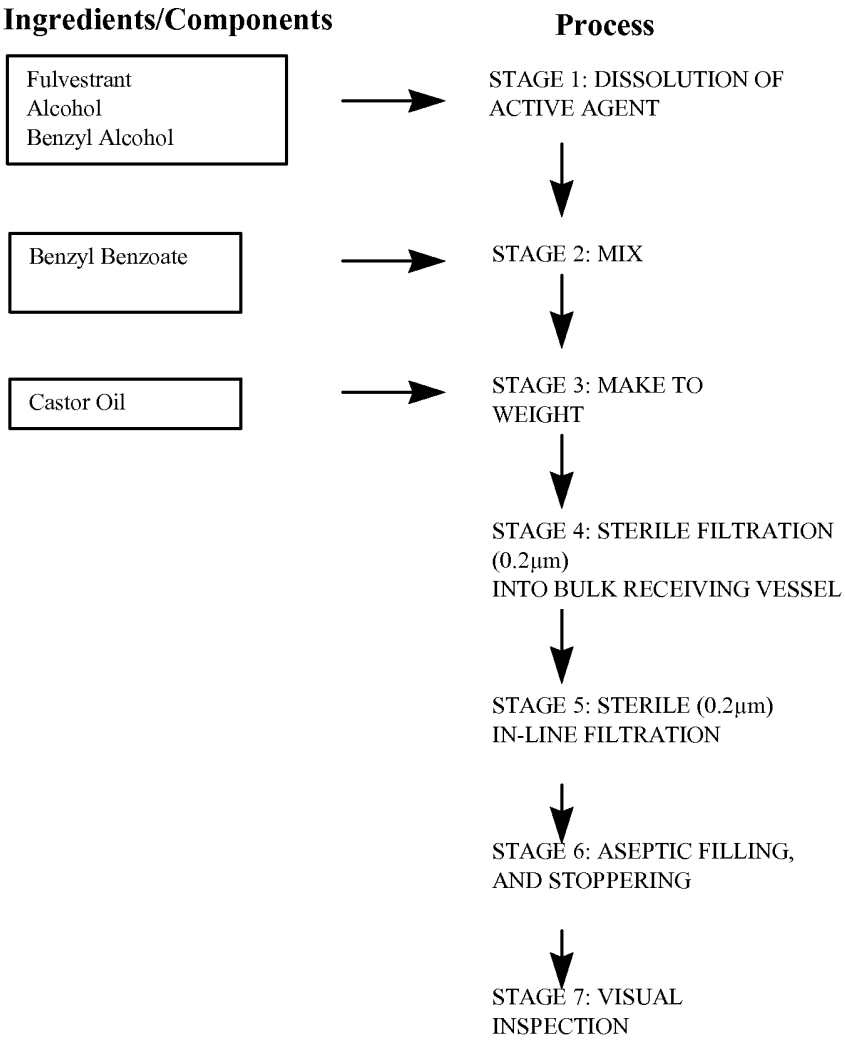

Figure 2

Electronic Patent Application Fee Transmittal

Application Number:	12285887
Filing Date:	15-Oct-2008
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Filer:	Donald J. Bird
Attorney Docket Number:	056291-5004-02

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 5 months with $0 paid	1255	1	2350	2350

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**2350**

Electronic Acknowledgement Receipt

EFS ID:	7135227
Application Number:	12285887
International Application Number:	
Confirmation Number:	1199
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	09629
Filer:	Donald J. Bird
Filer Authorized By:	
Attorney Docket Number:	056291-5004-02
Receipt Date:	03-MAR-2010
Filing Date:	15-OCT-2008
Time Stamp:	17:40:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2350
RAM confirmation Number	4396
Deposit Account	500310
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		056291-5004-SubstituteSpecification-Clean.pdf	217584 59458866282b262bd94b557102e80ff69a76e4aa	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	20
Abstract	21	21

Warnings:					
Information:					
2	Specification	056291-5004-SubstituteSpecification-Marked.pdf	184205 44acc667ccfffa425dc7c9d0f3e2455b24d192da	no	22
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	056291-5004-StatementAccomSubstituteSpecification.pdf	91194 a21304a1693605cb782d50e3929611c7bd54f64d	no	1
Warnings:					
Information:					
4	Drawings-only black and white line drawings	Figure1.pdf	50623 8f7fdc8fb2fb09a76e666027ded6c1d066e656e6	no	1
Warnings:					
Information:					
5	Drawings-only black and white line drawings	Figure2.pdf	56407 3050fd5f0cdb31d94da5f8cb7e1225c57d59bbbc	no	1
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	29814 237e4bf3c55936644445d0c482604308e86a54b9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	629827		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application No. 12/285,887

Second Substitute Specification

Clean Version

FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation Application of copending U.S. Patent Application No. 10/872,784, filed June 22, 2004, which claims benefit of U.S. Patent Application No. 09/756,291, filed January 9, 2001 which claims the benefit of Great Britain Application No. 0008837.7 filed April 12, 2000 and Great Britain Application No. 0000313.7, filed January 10, 2000, all of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Description of the Related Art

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for

the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

SUMMARY OF THE INVENTION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 below, and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits.

Figure 2 shows a process flow diagram associated with the Formulation Example.

DETAILED DESCRIPTION OF THE INVENTION

Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20

Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since

the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least 45mgml^{-1}.

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibly other organic solvents, for example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-

25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the

injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and difficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still achieved by the formulation of the invention.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25^{O}C

	% w/v							
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols

	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site

	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+

0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

A further feature of the invention is a method of treating a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

Preferably 5ml of the intramuscular injection is administered.

A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably treating breast cancer.

Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary

pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram of Figure 2.

Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol

10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

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ABSTRACT OF THE DISCLOSURE

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

Application No. 12/285,887

Second Substitute Specification

Marked Version

FORMULATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation Application of copending U.S. Patent Application No. 10/872,784, filed June 22, 2004, which claims benefit of U.S. Patent Application No. 09/756,291, filed January 9, 2001 which claims the benefit of Great Britain Application No. 0008837.7 filed April 12, 2000 and Great Britain Application No. 0000313.7, filed January 10, 2000, all of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Description of the Related Art

Oestrogen deprivation is fundamental to the treatment of many benign and malignant diseases of the breast and reproductive tract. In premenopausal women, this is achieved by the ablation of ovarian function through surgical, radiotherapeutic, or medical means, and, in postmenopausal women, by the use of aromatase inhibitors.

An alternative approach to oestrogen withdrawal is to antagonise oestrogens with antioestrogens. These are drugs that bind to and compete for oestrogen receptors (ER) present in the nuclei of oestrogen-responsive tissue. Conventional nonsteroidal antioestrogens, such as tamoxifen, compete efficiently for ER binding but their effectiveness is often limited by the partial agonism they display, which results in an incomplete blockade of oestrogen-mediated activity (Furr and Jordan 1984, May and Westley 1987).

The potential for nonsteroidal antioestrogens to display agonistic properties prompted the search for novel compounds that would bind ER with high affinity without activating any of the normal transcriptional hormone responses and consequent manifestations of oestrogens. Such molecules would be "pure" antioestrogens, clearly distinguished from tamoxifen-like ligands and capable of eliciting complete ablation of the trophic effects of oestrogens. Such compounds are referred to as Estrogen Receptor-Downregulators (E.R.D.). The rationale for

the design and testing of novel, pure antioestrogens has been described in: Bowler et al 1989, Wakeling 1990a, 1990b, 1990c. Wakeling and Bowler 1987, 1988.

Steroidal analogues of oestradiol, with an alkylsulphinyl side chain in the 7α position, provided the first examples of compounds devoid of oestrogenic activity (Bowler et al 1989). One of these, 7α-[9-(4,4,5,5,5-pentafluoropentyl sulphinyl)nonyl]oestra-1,3,5-(10)triene-3,17β-diol was selected for intensive study on the basis of its pure oestrogen antagonist activity and significantly increased antioestrogenic potency over other available antioestrogens. *In vitro* findings and early clinical experience with 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol have promoted interest in the development of the drug as a therapeutic agent for oestrogen-dependent indications such as breast cancer and certain benign gynaecological conditions.

7α-[9-(4,4,5,5,5-Pentafluoropentylsulphinyl)nonyl]oestra-1,3-5(10)-triene-3,17β-diol, or ICI 182,780, has been allocated the international non-proprietary name fulvestrant, which is used hereinafter. When referring to fulvestrant we include pharmaceutically-acceptable salts thereof and any possible solvates of either thereof.

Fulvestrant binds to ER with an affinity similar to that of oestradiol and completely blocks the growth stimulatory action of oestradiol on human breast cancer cells *in vitro*; it is more potent and more effective than tamoxifen in this respect. Fulvestrant blocks completely the uterotrophic action of oestradiol in rats, mice and monkeys, and also blocks the uterotrophic activity of tamoxifen.

Because fulvestrant has none of the oestrogen-like stimulatory activity that is characteristic of clinically available antioestrogens such as tamoxifen or toremifene, it may offer improved therapeutic activity characterised by more rapid, complete, or longer-lasting tumour regression; a lower incidence or rate of development of resistance to treatment; and a reduction of tumour invasiveness.

In intact adult rats, fulvestrant achieves maximum regression of the uterus at a dose which does not adversely affect bone density or lead to increased gonadotrophin secretion. If also true in humans, these findings could be of extreme importance clinically. Reduced bone density limits the duration of oestrogen-ablative treatment for endometriosis. Fulvestrant does not block hypothalamic ER. Oestrogen ablation also causes or exacerbates hot flushes and other menopausal symptoms; fulvestrant will not cause such effects because it does not cross the blood-brain barrier.

European Patent Application No. 0 138 504 discloses that certain steroid derivatives are effective antioestrogenic agents. The disclosure includes information relating to the preparation of the steroid derivatives. In particular there is the disclosure within Example 35 of the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, which compound is specifically named in Claim 4. It is also disclosed that the compounds of that invention may be provided for use in the form of a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically-acceptable diluent or carrier. It is stated therein that the composition can be in a form suitable for oral or parenteral administration.

Fulvestrant shows, along with other steroidal based compounds, certain physical properties which make formulation of these compounds difficult. Fulvestrant is a particularly lipophilic molecule, even when compared with other steroidal compounds, and its aqueous solubility is extremely low at around 10 $ngml^{-1}$ (this is an estimate from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute).

Currently there are a number of sustained release injectable steroidal formulations which have been commercialised. Commonly these formulations use oil as a solvent and wherein additional excipients may be present. Below in Table 1 are described a few commercialised sustained release injectable formulations.

In the formulations within Table 1 a number of different oils are used to solubilise the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol have been used. Volumes of oil needed to solubilise the steroid active ingredient are low. Extended release is achievable for periods from 1 to 8 weeks.

Table 1 - OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	BzBz	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone proprionate Testosterone phenylproprionate Testosterone isocaproate Testosterone decanoate	30mg 60mg 60mg 100mg	Androgen	Organon	ABPI Data Sheet Comp.1999	Arachis		0.1ml		1ml	3 weeks
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250mgml^{-1}	Progestogen	Schering HC	ABPI Data Sheet Comp.1999	Castor	up to 46%			1 or 2ml	1 week
TOCOGESTAN	Hydroxy progesterone enantate Progesterone α-Tocopherol	200mg 50mg 250mg	Progestogen	Theramax	Dict. Vidal 1999	Ethyl oleate	*40%			2ml	< 1week
TROPHOBOLENE	Estrapronicate Nandrolone undecanoate Hydroxyprogesterone heptanoate	1.3mg 50mg 80mg	Mixed	Theramax	Dict. Vidal 1997	Olive	45%			1ml	15 to 30 days
NORISTERAT	Norethisterone oenanthoate	200mg	Contraceptive	Schering HC	ABPI Data Sheet Comp.1999	Castor	YES			1ml	8 weeks
BENZO-GYNOESTRYL	Estradiol hexahydrobenzoate	5mg	Estradiol	Roussel	Dict. Vidal 1998	Arachis				1ml	1 week
PROGESTERONE -RETARD	Hydroxy progesterone caproate	250mgml^{-1}	Progestogen	Pharlon	Dict. Vidal 1999	Castor	YES			1 or 2ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate Hydroxyprogesterone caproate	5mgml^{-1} 250mgml^{-1}	Mixed	Schering HC	Dict. Vidal 1995	Castor	YES			1 or 2ml	1 - 2 weeks

PARABOLAN	Trenbolone	76mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75mg	45mg	1.5ml	2 weeks
DELESTROGEN	Estradiol valerate	$20mgml^{-1}$ $40mgml^{-1}$	Estradiol	BMS	J.Pharm. Sci (1964) 53(8) 891	Castor	78% 58%	20% 40%	2% 2%		
DELALUTIN	17-Hydroxy progesterone	$250mgml^{-1}$	Progestrogen	DMS	J.Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES	up to 2%		

BzBz = benzylbenzoate BzOH = benzylalcohol EtOH = ethanol Dict. Vidal = Dictionnaire Vidal
% are w/v and * approximate as measured directly from a single sample

described which comprises 50mg of fulvestrant, 400mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. Manufacture at a commercial scale of a formulation as described in US 5,183,814 will be complicated by the high alcohol concentration. Therefore, there is a need to lower the alcohol concentration in fulvestrant formulations whilst preventing precipitation of fulvestrant from the formulation.

SUMMARY OF THE INVENTION

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 below, and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits.

Figure 2 shows a process flow diagram associated with the Formulation Example.

DETAILED DESCRIPTION OF THE INVENTION

Table 2 shows the solubility of fulvestrant in a number of different solvents.

Table 2 - SOLUBILITY OF FULVESTRANT

SOLVENT	SOLUBILITY ($mgml^{-1}$ at 25°C)
Water	0.001
Arachis oil	0.45
Sesame oil	0.58
Castor oil	20

Miglyol 810	3.06
Miglyol 812	2.72
Ethyl oleate	1.25
Benzyl benzoate	6.15
Isopropyl myristate	0.80
Span 85 (surfactant)	3.79
Ethanol	>200
Benzyl Alcohol	>200

As can be seen fulvestrant is significantly more soluble in castor oil than any of the other oils tested. The greater solvating ability of castor oil for steroidal compounds is known and is attributed to the high number of hydroxy groups of ricinoleic acid, which is the major constituent of the fatty acids within the triglycerides present in castor oil - see (Riffkin et.al. J. Pharm. Sci., (1964), 53, 891).

However, even when using the best oil based solvent, castor oil, we have found that it is not possible to dissolve fulvestrant in an oil based solvent alone so as to achieve a high enough concentration to dose a patient in a low volume injection and achieve a therapeutically significant release rate. To achieve a therapeutically significant release rate the amount of fulvestrant needed would require the formulation volume to be large, at least 10 ml. This requires the doctor to inject an excessively large volume of formulation to administer a dose significantly high enough for human therapy.

Currently guidelines recommend that no more than 5mls of liquid is injected intramuscularly in a single injection. Pharmacologically active doses required for a 1 month long acting depot formulation of fulvestrant is around 250mg. Therefore, when dissolved in just castor oil, fulvestrant would need to be administered in at least 10ml of castor oil.

The addition of organic solvents in which fulvestrant is freely soluble, and which are miscible with castor oil, may be used, such as an alcohol. With the addition of high concentrations of an alcohol concentrations of >50mgml^{-1} of fulvestrant in a castor oil formulation is achievable, thereby giving an injection volumes of <5ml - see Table 3 below. We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 mgml^{-1} - see Table 3 below. The finding is surprising since

the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

Therefore, we present as a feature of the invention a pharmaceutical formulation comprising fulvestrant (preferably fulvestrant is present at 3-10%w/v, 4-9%w/v, 4-8%w/v, 4-7%w/v, 4-6%w/v and most preferably at about 5%w/v) in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol wherein the formulation is adapted for intramuscular administration and attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Another feature of the invention is a pharmaceutical formulation comprising fulvestrant in which the formulation is adapted for intra-muscular injection into a human and which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant, 30% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation which is capable after injection of attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks.

Further features of the invention include a pharmaceutical formulation adapted for intra-muscular injection comprising fulvestrant; 35% (preferably 30% and ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

For the avoidance of any doubt when using the term % weight per volume of formulation for the constituents of the formulation we mean that within a unit volume of the formulation a certain percentage of the constituent by weight will be present, for example a 1% weight per volume formulation will contain within a 100ml volume of formulation 1g of the constituent. By way of further illustration

% of x by weight per volume of formulation	weight of x in 1ml of formulation
30%	300mg
20%	200mg
10%	100mg
5%	50mg
1%	10mg

Preferred pharmaceutical formulations of the invention are as described above wherein:

1. The total volume of the formulation is 6ml, or less, and the concentration of fulvestrant is at least $45mgml^{-1}$.

2. The total amount of fulvestrant in the formulation is 250mg, or more, and the total volume of the formulation is 6ml, or less.

3. The total amount of fulvestrant in the formulation is 250mg and the total volume of the formulation is 5-5.25ml.

It is appreciated that in the formulation an excess of formulation may be included to allow the attendant physician or care giver to be able to deliver the required dose. Therefore, when a 5ml dose is required it would be appreciated that an excess of up to 0.25ml, preferably up to 0.15ml will also be present in the formulation. Typically the formulation will be presented in a vial or a prefilled syringe, preferably a prefilled syringe, containing a unit dosage of the formulation as described herein, these being further features of the invention.

Preferred concentrations of a pharmaceutically-acceptable alcohol present in any of the above formulations are; at least 3%w/v, at least 5%w/v, at least 7%w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 14% w/v, at least 15% w/v and, preferably, at least 16% w/v. Preferred maximal concentrations of pharmaceutically-acceptable alcohol present in the formulation are ;28% w/v or less, 22% w/v or less and 20% w/v or less.. Preferred ranges of pharmaceutically-acceptable alcohol present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 3-35%w/v, 4-35%w/v, 5-35%w/v, 5-32%w/v, 7-32%w/v, 10-30%w/v, 12-28%w/v, 15-25%w/v, 17-23%w/v, 18-22%w/v and ideally 19-21%w/v.

The pharmaceutically-acceptable alcohol may consist of one alcohol or a mixture of two or more alcohols, preferably a mixture of two alcohols. Preferred pharmaceutically-acceptable alcohols for parenteral administration are ethanol, benzyl alcohol or a mixture of both ethanol and benzyl alcohol, preferably the ethanol and benzyl alcohol are present in the formulation in the same w/v amounts. Preferably the formulation alcohol contains 10% w/v ethanol and 10% w/v benzyl alcohol.

The pharmaceutically-acceptable non-aqueous ester solvent may consist of one or a mixture of two or more pharmaceutically-acceptable non-aqueous ester solvents, preferably just one. A preferred pharmaceutically-acceptable non-aqueous ester solvent for parenteral administration is selected from benzyl benzoate, ethyl oleate, isopropyl myristate,isopropyl palmitate or a mixture of any thereof.

The ricinoleate vehicle should preferably be present in the formulation in a proportion of at least 30% weight per volume of the formulation, ideally at least 40% or at least 50% weight per volume of formulation.

It will be understood by the skilled person that the pharmaceutically-acceptable alcohol will be of a quality such that it will meet pharmacopoeial standards (such as are described in the US, British, European and Japanese pharmacopoeias) and as such will contain some water and possibly other organic solvents, for example ethanol in the US Pharmacopeia contains not less than 94.9% by volume and not more than 96.0% by volume of ethanol when measured at 15.56°C. Dehydrated alcohol in the US Pharmacopeia contains not less than 99.5% ethanol by volume when measured at 15.56°C.

Preferred concentrations of the pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are; at least 5% w/v, at least 8% w/v, at least 10% w/v, at least 11% w/v, at least 12% w/v, at least 13% w/v, at least 15% w/v, at least 16% w/v, at least 17% w/v, at least 18% w/v, at least 19% w/v and at least 20% w/v. Preferred maximal concentrations of the pharmaceutically-acceptable non-aqueous ester solvent are; 60% w/v or less, 50%w/v or less, 45% w/v or less, 40% w/v or less, 35% w/v or less, 30% w/v or less and 25% w/v or less. A preferred concentration is 15% w/v. Preferred ranges of pharmaceutically-acceptable non-aqueous ester solvent present in any of the above formulations are selected from any minimum or maximum value described above and preferably are; 5-60%w/v, 7-55%w/v, 8-50%w/v, 10-50%w/v, 10-45%w/v, 10-40%w/v, 10-35%w/v, 10-30%w/v, 10-

25%w/v, 12-25%w/v, 12-22%w/v, 12-20%w/v, 12-18%w/v, 13-17%w/v and ideally 14-16%w/v. Preferably the ester solvent is benzyl benzoate, most preferably at about 15%w/v.

It will be understood by the skilled person that the pharmaceutically-acceptable non-aqueous ester solvent will be of a quality that it will meet pharmacopoeial standards (such as described in the US, British, European and Japanese pharmacopoeias).

Preferred combinations of pharmaceutically-acceptable alcohol and pharmaceutically-acceptable non-aqueous ester solvent in the formulation are set out below:

Pharmaceutically-acceptable alcohol(%w/v)	**Pharmaceutically-acceptable non-aqueous ester (%w/v)**
10-30	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
17-23	5-60, 7-55, 8-50, 10-50, 10-45, 10-40, 10-35, 10-30, 10-25, 12-25, 12-22, 12-20, 12-18, 13-17 and ideally 14-16.
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-	10-35
3-35, 4-35, 5-35, 5-32, 7-32, 10-30, 12-28, 15-25, 17-23, 18-22 and ideally 19-21.	12-18
ethanol and benzyl alcohol, most preferably each at about 10%	benzyl benzoate, most preferably at about 15%

By the use of the term ricinoleate vehicle we mean an oil which has as a proportion (at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% w/v) of its composition as triglycerides of ricinoleic acid. The ricinoleate vehicle may be a synthetic oil or conveniently is castor oil, ideally of pharmacopoeial standards, as described above.

We have surprisingly found that the above formulations of the invention provide, after intra-muscular injection, satisfactory release of fulvestrant over an extended period of time.

This finding is indeed surprising for the following reasons.

1. Previously tested by the applicants have been intra-muscular injections of fulvestrant in the form of an aqueous suspension. We have found extensive local tissue irritation at the

injection site as well as a poor release profile. It is believed that the tissue irritation/inflammation was due to the presence of fulvestrant in the form of solid particles. The release profile appeared to be determined by the extent of inflammation/irritation present at the injection site and this was variable and difficult to control. Also the fulvestrant release rate was not sufficiently high to be clinically significant.

2. Our findings from studies using ^{14}C labelled benzyl alcohol show that it dissipates rapidly from the injection site and is removed from the body within 24 hours of administration.

It would be expected that ethanol will dissipate at least as quickly, if not more rapidly, from the injection site.

It is known that benzyl benzoate is metabolised by conjugation to glycine to form hippuric acid by the human liver and excreted into the urine - Martindale: The Extra Pharmacopoeia 32nd edition page 1103, and, therefore, it is unlikely that benzyl benzoate, when used, is present at the injection site during the whole of the extended release period.

We have found that despite the rapid elimination of the additional solubilising excipients, i.e. the alcohol and pharmaceutically-acceptable non-aqueous ester solvent, from the formulation vehicle and the site of injection after injection of the formulation, extended release at therapeutically significant levels of fulvestrant over an extended period can still achieved by the formulation of the invention.

By use of the term "therapeutically significant levels" we mean that blood plasma concentrations of at least 2.5 $ngml^{-1}$, ideally at least 3 $ngml^{-1}$, at least 8.5 $ngml^{-1}$, and up to 12 $ngml^{-1}$ of fulvestrant are achieved in the patient. Preferably blood plasma levels should be less than 15 $ngml^{-1}$.

By use of the term "extended release" we mean at least two weeks, at least three weeks, and, preferably at least four weeks of continuous release of fulvestrant is achieved. In a preferred feature extended release is achieved for 36 days. Preferably extended release of fulvestrant is for at least 2- 5 weeks and more preferably for the following periods (weeks) 2.5-5, 2.5-4, 3-4, 3.5-4 and most preferably for at least about 4 weeks.

It will be understood that the attendant physician may wish to administer the intramuscular injection as a divided dose, i.e. a 5ml formulation is sequentially administered in two separate injections of 2.5ml, this is a further feature of the invention

Simply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site.

Table 3 shows the solubility of fulvestrant in a castor oil vehicle additionally containing alcohols ethanol and benzyl alcohol with or without benzyl benzoate. The results clearly show the positive effect of benzyl benzoate on fulvestrant solubility in castor oil, despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

Table 3

Table 3 - EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25^{O}C

	% w/v							
Ethanol (96%)	5	5	10	10	10	10	15	15
Benzyl Alcohol	5	5	5	5	10	10	15	15
Benzyl Benzoate		15		15		15		15
Castor Oil	to 100	to100	to 100	to 100	to 100	to 100	to 100	to 100
Fulvestrant Solubility [$mgml^{-1}$]	27	36	46	54	45	65	76	102

The following Table 4 shows the solubility of fulvestrant in a range of oil based formulations which contain the same amounts of alcohol and benzyl benzoate but in which the oil is changed. The data also shows solubility of fulvestrant after removal of the alcohols.

Table 4

Solubility comparisons of fulvestrant in oil based formulations with and without alcohols

	Fulvestrant Solubility mg ml^{-1} @ 25°C	
Formulation [(a)]	Complete vehicle	Vehicle minus alcohols
Castor oil based	81.2	12.6
Miglyol 812-N based	86.8	1.7
Sesame seed/Castor oil (1:1) based	70.1	4.4
Sesame seed oil based	45.7	0.7
Arachis oil based	40.2	< 0.2

[(a)] **Complete Vehicle** Formulations comprised ethanol [96%](10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil. Excess fulvestrant was added to each solvent mixture and solubility determined.

Effect of formulation on precipitation of fulvestrant at the injection site

	Days						
Formulation [a]	2	3	4	7	10	30	51
Formulation F1 castor oil based	0	0	0	0	0	0	0
Formulation F2 Miglyol 812-N based	++ [b]	+++	+++	+++	+++	++	0
Formulation F3 sesame seed oil/castor oil based	+ [c]	++	++	+++	++	+	+

0, + , ++, +++ = Degree of precipitation (None detected, Mild, Moderate, Severe)

[a] Formulations comprised fulvestrant (5%), ethanol [96%] (10%), benzyl alcohol (10%) and benzyl benzoate (15%) made to volume with the stated oil.

[b] Mainly large needle shaped crystals

[c] Small needles and/or sheafs of crystals

Precipitation of fulvestrant and the release profile was determined with the above formulations in an *in vivo* rabbit study.

Figure 1 shows the release profile *in vivo* of the four formulations from the second part of Table 4 and shows the effect of the fixed oil component on fulvestrant plasma profile over five days following intramuscular administration in rabbits (data normalised to 50mg per 3kg; mean given; number of animals per timepoint = 8, plasma samples assayed for fulvestrant content using lc-ms/ms detection following solvent extraction). As can be seen the castor oil formulation showed a particularly even release profile with no evidence of precipitation of fulvestrant at the injection site.

Therefore we present as a further feature of the invention an extended release pharmaceutical formulation adapted for intramuscular injection comprising fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation and sufficient amount of a ricinoleate vehicle, taking into account the addition of any further optional pharmaceutically-acceptable excipients, so as to prepare a formulation of at least 45mgml^{-1} of fulvestrant.

A further feature of the invention is a pharmaceutical formulation adapted for intramuscular injection, as defined above, for use in medical therapy.

A further feature of the invention is a method of treating a benign or malignant diseases of the breast or reproductive tract, preferably treating breast cancer, by administration to a human in need of such treatment by intramuscular injection an extended release ricinoleate vehicle based pharmaceutical formulation comprising at least 45mgml^{-1} of fulvestrant; 35% (preferably 30% or ideally 25%) or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% (preferably at least 5% or ideally 10%) weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle per volume of formulation.

Preferably 5ml of the intramuscular injection is administered.

A further feature of the invention is use of fulvestrant in the preparation of a pharmaceutical formulation as describe hereinabove, for the treatment of a benign or malignant disease of the breast or reproductive tract, preferably treating breast cancer.

Additional excipients commonly used in the formulation field including, for example, an antioxidant preservative, a colorant or a surfactant may be used. A preferred optional excipient is a surfactant.

As described above fulvestrant is useful in the treatment of oestrogen-dependent indications such as breast cancer and gynaecological conditions, such as endometriosis.

In addition to fulvestrant another similar type of molecule is currently under clinical investigation. SH-646 (11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol) is also putatively a compound with the same mode of action as fulvestrant and has a very similar chemical structure. It is believed that the compound will also share with fulvestrant similar physical properties and therefore the current invention will also have application with this compound.

A further feature of the invention is a pharmaceutical formulation adapted for intra-muscular injection comprising 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol; 35% or less weight of a pharmaceutically-acceptable alcohol per volume of formulation, at least 1% weight of a pharmaceutically-acceptable non-aqueous ester solvent miscible within a ricinoleate vehicle per volume of formulation and a sufficient amount of a ricinoleate vehicle so as to prepare a formulation of at least 45mgml^{-1} of 11β-fluoro- 7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol.

Further features of the invention are those as described above but in which SH-646 is substituted for fulvestrant.

Formulation Example

Fulvestrant is mixed with alcohol and benzyl alcohol, stirring until completely dissolved. Benzyl benzoate is added and the solution is made to final weight with castor oil and stirred, (for convenience weight is used rather than volume by using the weight to volume ratio). The bulk solution is overlaid with Nitrogen. The solution is sterilised by filtration using one or two filters of 0.2μm porosity. The sterile filtrate is kept under a nitrogen overlay as it is filled under aseptic conditions into washed and depyrogenised, sterile primary containers, for example vials or pre-filled syringes. An overage is included in the primary

pack to facilitate removal of the dose volume. The primary packs are overlaid with sterile nitrogen, before aseptically sealing.

See also process flow diagram ~~below~~ of Figure 2.

Quantities of each component of the formulation is chosen according to the required formulation specification, examples are described above. For example quantities are added of each component to prepare a formulation which contains

10% weight per volume of benzyl alcohol

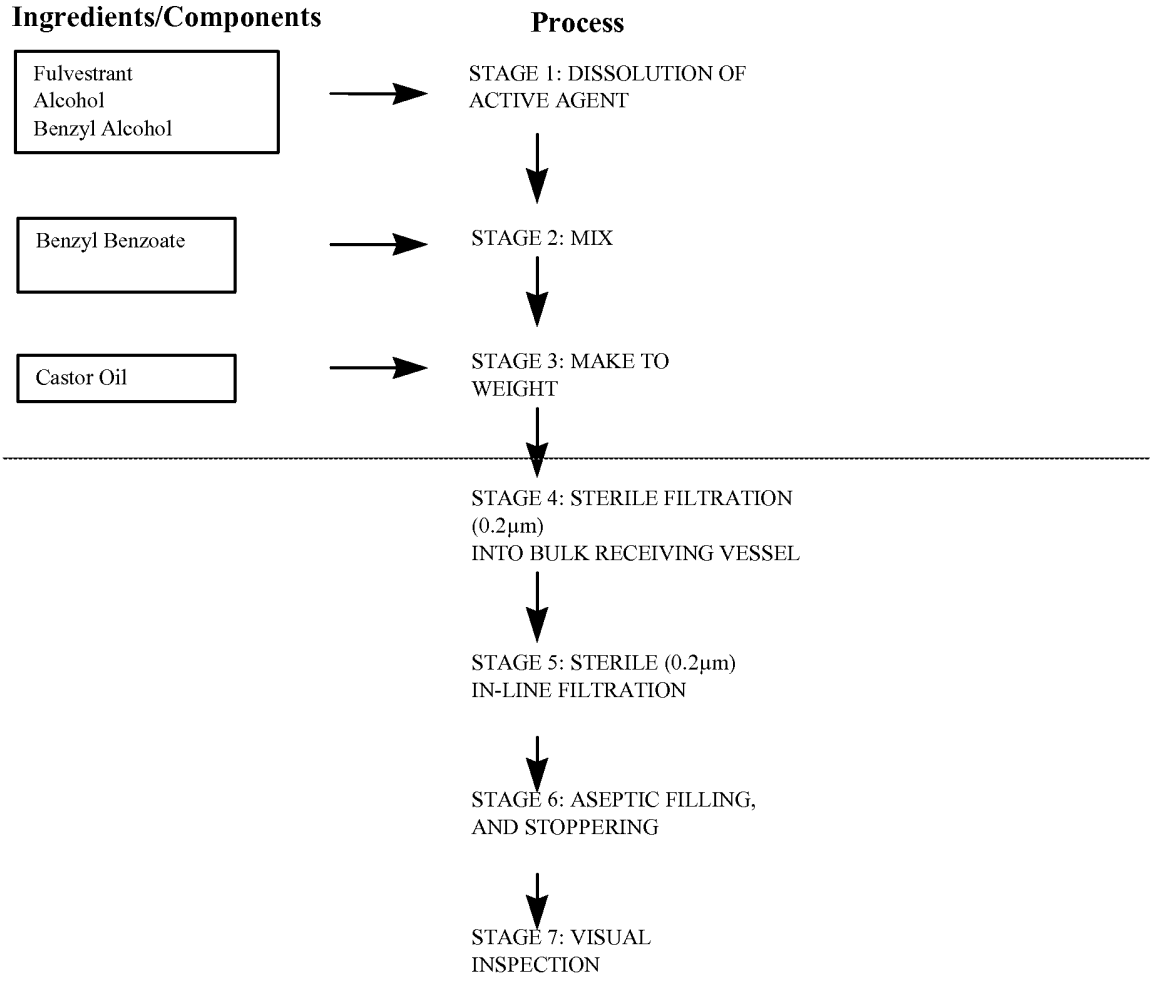
10% weight per volume of ethanol

15% weight per volume of benzyl benzoate

250mg of fulvestrant for each 5ml of finished formulation

and the remaining amount as castor oil

FLOW DIAGRAM OF MANUFACTURING



References

1. Bowler J, Lilley TJ, Pittam JD, Wakeling AE. Novel steroidal pure antioestrogens. Steroids 989; 5471-99.

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ABSTRACT OF THE DISCLOSURE

The invention relates to a novel sustained release pharmaceutical formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol, more particularly to a formulation adapted for administration by injection containing the compound 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol in solution in a ricinoleate vehicle which additionally comprises at least one alcohol and a non-aqueous ester solvent which is miscible in the ricinoleate vehicle.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/285,887	10/15/2008	1617	2754	056291-5004-02	23	2

CONFIRMATION NO. 1199

UPDATED FILING RECEIPT

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

Date Mailed: 03/11/2010

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 10/872,784 06/22/2004 PAT 7,456,160

Foreign Applications

UNITED KINGDOM 0008837.7 04/12/2000
UNITED KINGDOM 0000313.7 01/10/2000

If Required, Foreign Filing License Granted: 11/03/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/285,887**

Projected Publication Date: 06/17/2010

Non-Publication Request: No

Early Publication Request: No

Title

Formulation

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	056291-5004-02

CONFIRMATION NO. 1199

9629
MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

PUBLICATION NOTICE

OC000000042144085

Title: Formulation

Publication No.US-2010-0152149-A1
Publication Date:06/17/2010

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/285,887	10/15/2008	John R. Evans	056291-5004-02	1199

9629 7590 12/21/2010

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1628	
MAIL DATE	DELIVERY MODE
12/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/285,887	EVANS ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/872784.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/4/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is a continuation of US 10/872,784, filed 6/22/2004, now patent 7,456,160, which is a continuation of US 09/756,291, filed 1/9/2001, now patent 6,774,122. The instant application also claims the benefit of UNITED KINGDOM 0000313.7, filed 01/10/2000 and UNITED KINGDOM 0008837.7, filed 04/12/2000.

Claims 1-23 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dukes (EP 0 346 014) in view of Lehmann et al. (US Patent Re. 28,690), GB 1 569 286 (herein after referred as '286), Osborne et al., Journal of National Cancer Institute,

1995;87(10):746-750, and Remington (Remington's Pharmaceutical Sciences, 18th ed., 1990, page 219), all of the references are of record in the parent application.

Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, line 20-24).

Dukes does not expressly teach the dosage of fulvestrant to be 45mg. Dukes does not expressly teach the employment of benzyl benzoate, in the percent amount of 60% w/v or less, or 50% w/v or less, or 45% w/v or less, 40% w/v or less, or 35% w/v or less, or 30% w/v or less, 25% w/v or less, or 10-25% w/v, or 12-18% w/v, as part of the vehicle herein. Dukes does not expressly teach the total amount of the fulvestrant-containing composition administered. Dukes does not expressly teach weight amount of castor oil and benzyl alcohol. Dukes does not expressly teach the employment of ethanol as part of the vehicle herein. Dukes does not expressly teach the dosage of fulvestrant to be 250mg. Dukes does not expressly teach the plasma concentration of fulvestrant herein.

Lehmann et al. teaches that benzyl benzoate and castor oil are well-known solvent useful as conventional carriers for steroids (See col. 1, line 21-26).

'286 teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in a ratio of 6:4 (See page 1, line 17).

Osborne et al. teaches fulvestrant as useful in treating human breast cancer (See pages 747- 748, Result Section).

Remington teaches that ethanol is one of the most commonly used solvents in pharmaceutical industry (See page 219).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy in the vagina.

One of ordinary skill in the art would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant, in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy or treating breast cancer because fulvestrant is known to be useful in treating urogenital atrophy, a benign disease of the female reproductive tract in the vagina and breast cancer. Castor oil and benzyl alcohol are known to be effective as vehicle for fulvestrant. Ethanol is a commonly used pharmaceutical solvent. Benzyl benozate is known to be effective as solvent for steroidal compounds. Since fulvestrant is a estrogen derivative, benzyl benzoate would be reasonably expected to be useful as a solvent for fulvestrant. Therefore, combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expected to be useful in formulating a pharmaceutical composition. Furthermore, employing such

fulvestrant-containing composition to treat urogenital atrophy in vagina would be reasonably expected to be effective. Moreover, the optimization of result effect parameters (e.g., amount of excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary.

One of ordinary skill in the art would have been motivated to maintain the plasma concentration of fulvestrant herein because maintaining the therapeutic plasma level of the active compounds would be considered obvious as being within the purview of the skilled artisan, absent evidence to the contrary. Furthermore, the fulvestrant composition is known to be administered through injection, therefore, putting the composition into a syringe for delivering the fulvestrant composition would be considered obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,774,122 ('122). Although the conflicting claims are not identical, they are not patentably distinct from each other because '122 teaches the method of treating hormonal dependent benign or malignant disease of reproductive tract by employing the herein claimed composition.

Claims 21-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 7,456,160 ('160). Although the conflicting claims are not identical, they are not patentably distinct

from each other because '160 teaches the method of treating hormonal dependent benign or malignant disease of reproductive tract by employing the herein claimed composition.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1628

/San-ming Hui/
Primary Examiner, Art Unit 1628

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
12285887 7	12285887	EVANS ET AL.
	Examiner	Art Unit
	San-ming Hui	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/19/2010								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
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	20	✓								
	21	✓								
	22	✓								
	23	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
12285887	12285887	EVANS ET AL.
	Examiner	**Art Unit**
	San-ming Hui	1628

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**
514	177, 178	12/19/10	SH

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST and inventor search in PALM	12/19/10	SH

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

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BIB DATA SHEET

CONFIRMATION NO. 1199

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/285,887	10/15/2008	514	1628	056291-5004-02

APPLICANTS

John R. Evans, Macclesfield, UNITED KINGDOM;
Rosalind U. Grundy, Macclesfield, UNITED KINGDOM;

**** CONTINUING DATA ***************************

This application is a CON of 10/872,784 06/22/2004 PAT 7,456,160

**** FOREIGN APPLICATIONS ***************************

UNITED KINGDOM 0008837.7 04/12/2000
UNITED KINGDOM 0000313.7 01/10/2000

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

11/03/2008

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/SAN-MING R HUI/ Examiner's Signature	☐ Initials	UNITED KINGDOM	1	23	2

ADDRESS

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004
UNITED STATES

TITLE

Formulation

FILING FEE RECEIVED		
2754	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	76861	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L2	310	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L3	2043	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L4	2	"4659516".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L5	6	"346014".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L6	13851	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L7	1744228	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L8	7012	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33

L9	4	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (estrogen or estradiol or estrone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L10	7	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L11	13	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L12	1562	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L13	2	"6774122".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L14	910	514/177.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L15	1322	514/178.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L16	1979621	castor oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L17	76861	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33

L18	310	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L19	2043	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L20	13851	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L21	1744228	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L22	7012	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L23	7	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L24	13	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L25	1562	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L26	76861	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33

L27	4282	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L28	2482	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L29	1306	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L30	3	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L31	2692	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L32	2692	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L33	76861	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L34	310	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L35	2043	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33

L36	2	"4659516".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L37	6	"346014".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L38	13851	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L39	1744228	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L40	7012	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L41	4	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (estrogen or estradiol or estrone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L42	7	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L43	13	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L44	1562	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33

L45	76861	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L46	4282	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L47	2482	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L48	1306	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L49	3	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L50	2692	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L51	81494	breast adj cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L52	1783	breast adj cancer and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L53	281	breast adj cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33

L54	1131	cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:33
L55	2	"7456160".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:38
L56	2	"6,774,122".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/12/19 22:38

EAST Search History (Interference)

<This search history is empty>

12/19/10 10:49:53 PM
C:\Documents and Settings\SHui\My Documents\EAST\Workspaces\12-285887.wsp

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary)	Attorney Docket No. **056291-5004-02**	Application No. **12/285,887**
	Applicants: **John R. EVANS *et al.***	
PTO Form 1449 June 4, 2009	Filing Date: **October 15, 2008**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date
	1.	US 3,164,520	January 5, 1965	Huber			
	2.	US 4,212,863	July 15, 1980	Cornelius			
	3.	US 4,388,307	June 14, 1983	Cavanak			

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation
	4.	EP 0310542A1	April 5, 1989	EPO			Yes

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	5.	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
	6.	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
	7.	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
	8.	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
	9.	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 [pages 238-255 provided] (1998)
	10.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
	11.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
	12.	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
	13.	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

Examiner	/San Ming Hui/	Date Considered	12/19/2010

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

DB1/63065447.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.H./

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) PTO Form 1449 June 4, 2009	Attorney Docket No. **056291-5004-02**	Application No. **12/285,887**
	Applicants: **John R. EVANS *et al.***	
	Filing Date: **October 15, 2008**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date
	1.	2,822,316	February 4, 1958	Richter et al.			
	2.	2,983,649	May 9, 1961	Ercoli et al.			
	3.	3,541,209	November 17, 1970	Neumann et al.			
	4.	RE 28,690	January 20, 1976	Lehmann et al.			
	5.	4,048,309	September 13, 1977	Chen et al.			
	6.	4,048,310	September 13, 1977	Chen et al.			
	7.	4,659,516	April 21, 1987	Bowler et al.			
	8.	4,888,331	December 19, 1989	Elger et al.			
	9.	5,095,129	March 10, 1992	Ottow et al.			
	10.	5,183,814	February 2, 1993	Dukes			
	11.	5,484,801	January 16, 1996	Al-Razzak et al.			
	12.	5,733,902	March 31, 1998	Schneider			
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	14.	20010006963	July 5, 2001	Lachnit-Fixson et al.			

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		Document No.	Date	Country	Class	Sub-Class	Translation
	15.	EP 0138504	Apr., 1985	EP			
	16.	EP 0346014	Dec., 1989	EP			
	17.	EP 0819431	Mar., 1999	EP			
	18.	EP 0905143	Mar., 1999	EP			
	19.	FR 6241	Sep., 1968	France			Abstract
	20.	GB 817241	Jul., 1959	GB			
	21.	GB 1126892	Sep., 1968	GB			
	22.	GB 1207571	Oct., 1970	GB			
	23.	GB 1569286	Jun., 1980	GB			
	24.	JP 43-27327	Nov., 1992	Japan			
	25.	JP 09-208496	Dec., 1997	Japan			Abstract
	26.	JP 10-203982	Apr., 1998	Japan			
	27.	JP 10-152438	Jun., 1998	Japan			Abstract
	28.	JP 11-501649	Feb., 1999	Japan			
	29.	JP 11-158200	Jun., 1999	Japan			
	30.	SU 549118	Mar., 1977	Soviet Union			Abstract
	31.	SU 676284	Jul., 1979	Soviet Union			Abstract
	32.	WO 95/12383	May., 1995	WIPO			Abstract

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

Examiner	Date Considered

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DB1/63064901.1 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.H./

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) PTO Form 1449 June 4, 2009	Attorney Docket No. **056291-5004-02**	Application No. **12/285,887**
	Applicants: **John R. EVANS *et al.***	
	Filing Date: **October 15, 2008**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation
	33.	WO 96/19997	Jul., 1996	WIPO			Abstract
	34.	WO 97/21440	Jun., 1997	WIPO			
	35.	WO 97/37653	Oct., 1997	WIPO			Abstract
	36.	WO 97/40823	Nov., 1997	WIPO			
	37.	WO 98/11902	Mar., 1998	WIPO			Abstract
	38.	WO 99/27906	Jun., 1999	WIPO			
	39.	ZA 681014	Feb., 1968	South Africa			
	40.	ZA 682530	Apr., 1968	South Africa			

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	41.	Anschel, "Lösungsmittel und Lösungsvermittler in Injektionen", Pharm, Ind., 1965, Vol. 27 (11a), pp. 781-787
	42.	Davis et al., "17-Alpha-Hydroxyprogesterone-Caproate:…with Chemically Pure Progesterone", J. Clin. Endocrinol. And Metabolism, 1955, Vol. 15, pp. 923-930
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	45.	Howell et al., "Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer", British Journal of Cancer, 1996, Vol. 74, pp. 300-308
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	47.	Mackey et al, "Tolerability of intramuscular injections of testosterone ester in oil vehicle", Human Reproduction, vol. 10, no. 4, pp, 869-865, 1995
	48.	Martindale, 32nd Ed., "Alcohol", Pharmaceutical Press, 1999, pp. 1099-1101
	49.	Martindale, 32nd Ed., "Benzoates" and "Benzyl Alcohol"; Pharmaceutical Press, 1999, pp. 1102-1104
	50.	Martindale, 32nd Ed., "Caster Oil"; 32nd Ed., Pharmaceutical Press, 1999, p. 1560
	51.	Migally, "Effect of Castor Oil and Benzyl Benzoate Used as a Vehicle for Antiandrogens on the Adrenal Cortex", Archives of Andrology 2, 1979 pp. 365-369
	52.	Osborne et al., "Comparison of the Effects of a Pure Steroidal Antiestrogen With Those of Tamoxifen in a Model of Human Breast Cancer", Journal of the National Cancer, May 1995, Vol. 87, No. 10, pp. 746-750
	53.	Pellegrino, "Use of 17 α Hydroxyprogesterone Caproate in Threatened Abortion", Current Therapeutic Research, Vol. 4, No. 6, June, 1962, pp. 301-305
	54.	Piver et al., "Medroxyprogesterone Acetate (Depo-Provera) vs. . . . Women with Metastatic Endometrial Adenocarcinoma", Cancer, Vol. 45, American Cancer Society, 1980, pp. 268-272
	55.	Remington's Pharmaceutical Sciences, 18th ed., 1990, p. 219

Examiner	Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

DB1/63064901

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.H./

INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) PTO Form 1449 June 4, 2009	Attorney Docket No. **056291-5004-02**	Application No. **12/285,887**
	Applicants: **John R. EVANS *et al.***	
	Filing Date: **October 15, 2008**	Group Art Unit: **1617**

U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

	56.	Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, pp. 891-895
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	58.	Sawada et al., "Estrogen Receptor Antagonist ICII82,780 Exacerbates Ischemic Injury in Female Mouse", Journal of Cerebral Blood Flow and Metabolism, Vol. 20. No. 1, 2000, pp. 112-118.
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	61.	Vidal, Le Dictionnaire, "Parabolan", 1997, pg. 1245
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Examiner	Date Considered
/San Ming Hui/	12/19/2010

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.H./

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
John R. Evans et al.	Group Art Unit: 1628
Application No.: 12/285,887	Examiner: HUI, San Ming R.
Filed: October 15, 2008	
For: FORMULATION	Confirmation No.: 1199

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REVOCATION OF POWER OF ATTORNEY
STATEMENT UNDER 37 C.F.R. § 3.73(b)
AND GRANT OF NEW POWER OF ATTORNEY

The undersigned, a representative authorized to sign on behalf of the assignee owning all of the interest in this patent application, hereby revokes all previous powers of attorney or authorization of agent granted in this application before the date of execution hereof.

As required by 37 C.F.R. § 3.73(b), the undersigned verifies that AstraZeneca AB is the assignee of the entire right, title, and interest in the patent application identified above by virtue of an assignment from the inventors recorded in parent Application No. 10/872,784 in the U.S. Patent and Trademark Office at Reel 015906, Frame 0402.

The undersigned representative of the Assignee hereby grants its power of attorney to the patent practitioners associated with **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P., Customer Number 22,852,** to prosecute

this application and to transact all business in the Patent and Trademark Office connected therewith, and to receive the Letters Patent.

Please send all future correspondence concerning this application to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Customer No. 22,852.

Dated: 27 May 2011 By: _____

Name: DR ALLEN F GILES

Title: AUTHORISED REPRESENTATIVE

AstraZeneca AB

Electronic Acknowledgement Receipt

EFS ID:	10182478
Application Number:	12285887
International Application Number:	
Confirmation Number:	1199
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	09629
Filer:	Carlos M. Tellez
Filer Authorized By:	
Attorney Docket Number:	056291-5004-02
Receipt Date:	27-MAY-2011
Filing Date:	15-OCT-2008
Time Stamp:	13:09:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	Executed_power_11285-0056.pdf	36929 1df66963cd97026c75078f395b2ba7dac73a9f6a	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	36929

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/285,887	10/15/2008	John R. Evans	11285.0056-00000

CONFIRMATION NO. 1199

POA ACCEPTANCE LETTER

22852
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

OC000000048042566

Date Mailed: 06/07/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/27/2011.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/snguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
John R. Evans et al.	)	Group Art Unit: 1628
	)	
Application No.: 12/285,887	)	Examiner: HUI, San Ming R.
	)	
Filed: October 15, 2008	)	Confirmation No.: 1199
	)	
For: FORMULATION	)	**VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE AND AMENDMENT UNDER 37 C.F.R. § 1.111 AND PETITION FOR EXTENSION OF TIME

In reply to the non-final Office Action mailed December 21, 2010 ("Office Action"), and pursuant to 37 C.F.R. § 1.111, Applicants hereby respectfully request reconsideration of this application in view of the following amendments and remarks. Applicants hereby petition for a three-month extension of time to respond to the Office Action. The requisite fee is being paid concurrently with this Response.

Amendments to the Claims are reflected in the listing of claims, which starts on page 2 of this paper. **Remarks** follow the amendment sections of this paper and start on page 9.

AMENDMENTS TO THE CLAIMS

Please add new claims 24-53. Please also cancel claims 1-23 without prejudice or disclaimer. This listing of claims will replace all prior versions and listings of claims in the application.

Claims 1-23 (Cancelled)

24. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation comprising:

at least 45 $mgml^{-1}$ of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

25. (New) The method of claim 24, wherein the ethanol and benzyl alcohol are present in the same weight/volume amounts.

26. (New) The method of claim 24, wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.

27. (New) The method of claim 24, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.

28. (New) The method of claim 24, wherein the therapeutically significant blood plasma fulvestrant concentration is attained for at least 4 weeks.

29. (New) The method of claim 24, wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation.

30. (New) The method of claim 24, wherein the method further comprises once monthly administration of the formulation.

31. (New) The method of claim 24, wherein the formulation comprises:

about 50 $mgml^{-1}$ of fulvestrant;

about 10% w/v of ethanol;

about 10% w/v of benzyl alcohol; and

about 15% w/v of benzyl benzoate;

wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.

32. (New) The method of claim 31, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.

33. (New) The method of claim 32, wherein the therapeutically significant blood plasma fulvestrant concentration is attained for at least 4 weeks.

34. (New) The method of claim 33, wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation.

35. (New) The method of claim 34, wherein the method further comprises once monthly administration of the formulation.

36. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation consisting essentially of:

at least 45 $mgml^{-1}$ of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

37. (New) The method of claim 36, wherein the ethanol and benzyl alcohol are present in the same weight/volume amounts.

38. (New) The method of claim 36, wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.

39. (New) The method of claim 36, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.

40. (New) The method of claim 36, wherein the therapeutically significant blood plasma fulvestrant concentration is attained for at least 4 weeks.

41. (New) The method of claim 36, wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation.

42. (New) The method of claim 36, wherein the method further comprises once monthly administration of the formulation.

43. (New) The method of claim 36, wherein the formulation consists essentially of:

about 50 $mgml^{-1}$ of fulvestrant;

about 10% w/v of ethanol;

about 10% w/v of benzyl alcohol; and

about 15% w/v of benzyl benzoate;

wherein the therapeutically significant blood plasma fulvestrant concentration is at least 8.5 $ngml^{-1}$.

44. (New) The method of claim 43, wherein the hormonal dependent benign or malignant disease of the breast or reproductive tract is breast cancer.

45. (New) The method of claim 44, wherein the therapeutically significant blood plasma fulvestrant concentration is attained for at least 4 weeks.

46. (New) The method of claim 45, wherein the method comprises administering intramuscularly to a human in need of such treatment 5 mL of the formulation.

47. (New) The method of claim 46, wherein the method further comprises once monthly administration of the formulation.

48. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment 5 – 5.25 mL of a formulation comprising:

4 - 6% w/v of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

49. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising monthly intramuscular administration to a human in need of such treatment of a formulation comprising:

4 - 6% w/v of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

50. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising monthly intramuscular administration to a human in need of such treatment of a formulation comprising:

4 - 6% w/v of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the formulation is administered in a divided dose; and

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

51. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment 5 – 5.25 mL of a formulation consisting essentially of:

4 - 6% w/v of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

52. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising monthly intramuscular administration to a human in need of such treatment of a formulation consisting essentially of:

4 - 6% w/v of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

53. (New) A method for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising monthly intramuscular administration to a human in need of such treatment of a formulation consisting essentially of:

4 - 6% w/v of fulvestrant;

a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol;

12 - 18% w/v of benzyl benzoate; and

a sufficient amount of castor oil vehicle;

wherein the formulation is administered in a divided dose; and

wherein the method achieves a therapeutically significant blood plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks.

REMARKS

I. Status of the claims and amendments

Upon entry of the instant amendments, claims 24-53 will be pending in this application. Claims 1-23 are being cancelled in this Response without prejudice or disclaimer. New claims 24-53 are being added in this Response. Claims 24-35 and 48-50 are directed to methods for treating a hormonal dependent benign or malignant disease of the breast or reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation *comprising* various components. Claims 36-47 and 51-53 are identical to claims 24-35 and 48-50 except that the phrase "formulation *consisting essentially of*" replaces the phrase "formulation *comprising*" the various components.

New **claim 24** finds support, for example, in original claim 21. The recitation in claim 24 regarding "at least 45 mg ml^{-1} of fulvestrant" finds support, for example, in the specification at ¶ [0028].[1] The recitation regarding "a mixture of from 17 – 23% w/v of ethanol and benzyl alcohol" finds support, for example, in the specification at ¶¶ [0035], [0036], and [0042]. The recitation regarding "12 - 18% w/v of benzyl benzoate" finds support, for example, in the specification at ¶¶ [0040] and [0042]. The recitation regarding "a sufficient amount of castor oil vehicle" finds support, for example, in the specification at ¶ [0027]. The recitation regarding "a therapeutically significant blood

[1] Unless otherwise specified, all citations to the instant specification refer to the pagination from the published application US 2010/0152149.

plasma fulvestrant concentration of at least 2.5 $ngml^{-1}$ for at least two weeks" finds support, for example, in the specification at ¶¶ [0027] and [0051].

New **claim 25** finds support, for example, in the specification at ¶ [0036]. New **claim 26** finds support, for example, in the specification at ¶ [0051]. New **claim 27** finds support, for example, in the specification at ¶ [0064]. New **claim 28** finds support, for example, in the specification at ¶ [0052]. New **claim 29** finds support, for example, in the specification at ¶ [0063]. New **claim 30** finds support, for example, in the specification at ¶ [0023]. New **claim 31** finds support, for example, in the specification at ¶ [0051] and the "Formulation Example" (*e.g.*, ¶¶ [0072] to [0076]). New **claim 32** finds support, for example, in the specification at ¶ [0064]. New **claim 33** finds support, for example, in the specification at ¶ [0052]. New **claim 34** finds support, for example, in the specification at ¶ [0063]. New **claim 35** finds support, for example, in the specification at ¶ [0023].

Claims 48-50 share various limitations with claim 24, for which support has been identified above. The recitation in **claim 48** regarding administration of "5 – 5.25 mL" of formulation finds support, for example, in the specification at ¶ [0034]. The recitation in **claim 48** regarding "4 - 6% w/v of fulvestrant" finds support, for example, in the specification at ¶ [0025]. The recitation in **claim 49** regarding "monthly intramuscular administration" finds support, for example, in the specification at ¶ [0023]. The recitation in **claim 50** regarding "the formulation [being] administered in a divided dose" finds support, for example, in the specification at ¶ [0053].

Because **claims 36-47 and 51-53** are identical to claims 24-35 and 48-50 except for the transitional phrase ("consisting essentially of" instead of "comprising"), the same

disclosure from the instant specification cited above for claims 24-35 and 48-50 provides support for claims 36-47 and 51-53. The instant amendments do not add new matter.

II. Rejection under 35 U.S.C. § 103

The Office rejected claims 1-23 under 35 U.S.C. § 103(a) as being unpatentable over European Patent Specification No. EP 0 346 014 ("*Dukes*") in view of US Reissue Patent No. 28,690 ("*Lehmann*"), Great Britain Patent Specification No. GB 1 569 286 ("GB 1 569 286"), Osborne et al., Journal of National Cancer Institute, 87(10):746-750 (1995) ("*Osborne*"), and Remington's Pharmaceutical Sciences, 18th ed., p. 219 (1990) ("*Remington*").

Applicants cancelled claims 1-23 in the instant Response. Thus, this rejection is now moot. However, in an effort to advance prosecution, and to the extent that the Office is considering applying the arguments from the outstanding obviousness rejection to the newly added claims, Applicants will address the rejections in the Office Action below.

According to the Office, *Dukes* teaches that "antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina." Office Action at 3. The Office further argues that *Dukes* "teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol." *Id.* The Office acknowledges, however, that among other deficiencies, *Dukes* "does not expressly teach the employment of benzyl benzoate . . . as part of the vehicle herein." *Id.*

In an attempt to cure the shortcomings in *Dukes*, the Office cites *Lehmann* as teaching "that benzyl benzoate and castor oil are well-known solvent useful as conventional carriers for steroids." Office Action at 3. In the Office's view GB 1 569 286 "teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in a ratio of 6:4" (*id.*); *Osborne* "teaches fulvestrant as useful in treating human breast cancer" (*id.* at 4); and *Remington* teaches "that ethanol is one of the most commonly used solvents in pharmaceutical industry" (*id.*).

The Office concludes that:

> One of ordinary skill in the art would have been motivated to employ benzyl benzoate, ethanol, castor oil, and benzyl alcohol, in the herein claimed weight percent, with fulvestrant, in the dosage herein, in a method of treating postmenopausal symptoms such as urogenital atrophy or treating breast cancer because fulvestrant is known to be useful in treating urogenital atrophy, a benign disease of the female reproductive tract in the vagina and breast cancer.

Office Action at 4. According to the Office:

> [C]ombining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expected to be useful in formulating a pharmaceutical composition.

Office Action at 4. The Office further argues that "the optimization of result effect[ive] parameters (e.g., amount of excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan, absent evidence to the contrary." *Id.* at 5. Applicants respectfully traverse this rejection.

II.A One of ordinary skill in the art would not have combined the cited references in the manner proposed in the rejection

The Office relies on *Dukes* to argue that formulations comprising fulvestrant "in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol" were known in the art. Office Action at 3. The Office then states that one of ordinary skill in the art would have added ethanol and benzyl benzoate to *Dukes* formulation to arrive at the formulation recited in the claims. *Id.* The Office, however, provides no explanation for why one of ordinary skill in the art would have modified *Dukes* formulation in the proposed manner. As will be explained below, one of ordinary skill in the art would not have modified *Dukes* formulation at least because the addition of benzyl benzoate would have been expected to reduce the solubility of fulvestrant in the formulation. Because fulvestrant is difficult to formulate, one of ordinary skill in the art would not have prepared a formulation in which fulvestrant was expected to have a lower solubility than that in the initial formulation. *See, e.g.*, specification at ¶ [0014].

The passage from *Dukes* cited by the Office as disclosing fulvestrant formulations indicates that when administering a pure antiestrogen by periodic intramuscular injection, an oily solution of the pure antiestrogen "containing arachis or castor oil [and] an alcohol such as benzyl alcohol" is preferred. *Dukes* at 7, ll. 19-23. *Dukes* also discloses two different formulations of fulvestrant in its working examples. Example 1 from *Dukes* discloses fulvestrant "in a mixture of propylene glycol: ethanol: water: poloxamer 407." *Dukes* at 8, ll. 35-37. Example 2 discloses a formulation "contain[ing] 50 mg of [fulvestrant], 400 mg of benzyl alcohol and sufficient castor oil to

bring the solution to a volume of 1 ml" ("*Dukes* castor oil formulation"). *Dukes* at 9, ll. 21-23.

No explanation for why one of ordinary skill in the art would have modified the *Dukes* castor oil formulation in any way is set forth in the Office Action. The Office seems to imply that one of ordinary skill in the art would have added ethanol and benzyl benzoate to *Dukes* castor oil formulation simply because ethanol and benzyl benzoate were "known to be useful as commonly used solvents." Office Action at 3. The focus in an obviousness rejection, however, is not on what one of ordinary skill in the art *could* have done, but rather "on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person *would have reasonably expected to have been able to do* in view of that knowledge." M.P.E.P. § 2141.II (emphasis added).

In this regard, one of ordinary skill in the art attempting to improve any of the *Dukes* formulations would have determined the solubility of fulvestrant in any test solvent before adding the solvent to the formulation. See, for example, Table 2 of the instant application, which reports solubility of fulvestrant in castor oil, benzyl alcohol, ethanol, and benzyl benzoate. According to Table 2, the solubility of fulvestrant in benzyl benzoate is 6.15 $mgml^{-1}$, whereas the corresponding solubility in benzyl alcohol is >200 $mgml^{-1}$. Thus, based on solubility data, one of ordinary skill in the art would have realized that fulvestrant is more than one order of magnitude more soluble in benzyl alcohol than in benzyl benzoate. Therefore, incorporating benzyl benzoate into *Dukes* castor oil formulation at the expense of reducing the concentration of benzyl alcohol, as would be required to arrive at the formulation recited in the instant claims

starting from *Dukes* disclosure, would have been expected to *decrease* the solubility of fulvestrant in the resulting formulation. None of the references cited by the Office suggests otherwise. As mentioned before, decreasing the solubility of fulvestrant in a given formulation would exacerbate the problem of finding a suitable formulation for fulvestrant.

Thus, none of the cited references would have suggested to one of ordinary skill in the art the modification of any of *Dukes* formulations by the addition of benzyl benzoate. For at least this reason, the Office has not made a *prima facie* case of obviousness and Applicants respectfully request that this rejection be withdrawn.

II.B The Office has not made the necessary factual findings to support a conclusion of obviousness

By arguing that one of ordinary skill in the art would have added ethanol and benzyl benzoate to *Dukes* castor oil formulation simply because the additional solvents were known in the art (Office Action at 3), the Office seems to be basing the rejection in a "combination of prior art elements" rationale. *See, e.g.*, M.P.E.P. § 2143.A. However, an obviousness rejection under this rationale requires, among other requisites: (1) "a finding that . . . each element [in the combination] merely performs the same function as it does separately" and (2) "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." *Id.* The Office has not met either of these requirements.

First, the Office has not shown that the solvents proposed to be added to *Dukes* castor oil formulation, ethanol and benzyl benzoate, would have performed the same function in the resulting formulation as they performed separately. As explained in the

previous section, the addition of benzyl benzoate to a given fulvestrant formulation would have been expected to reduce the solubility of fulvestrant in the original formulation. Table 3 in the instant specification compares the solubility of fulvestrant in various formulations comprising ethanol, benzyl alcohol, and castor oil in the presence and absence of benzyl benzoate. In each case, the solubility of fulvestrant in the solution containing benzyl benzoate *increased* compared to the solubility of fulvestrant in the corresponding formulation without benzyl benzoate. *Id.* The trend shown in Table 3 demonstrates that benzyl benzoate is *not* "perform[ing] the same function as it does separately."

Second, because the addition of benzyl benzoate does not decrease the solubility of fulvestrant in the resulting formulation, as would have been expected, the Office cannot find that "one of ordinary skill in the art would have recognized that the results of the combination were predictable."

Even under an "obvious to try" rationale, the Office needs to show that "one of ordinary skill in the art could have pursued the known potential solutions *with a reasonable expectation of success*." M.P.E.P. § 2143.E. In the instant case, as shown in Section II.A above, one of ordinary skill in the art could not have expected that adding benzyl benzoate to *Dukes* castor oil formulation, while decreasing the amount of benzyl alcohol as would be required to arrive at the formulation recited in the instant claims, would have resulted in a suitable fulvestrant formulation.

For the foregoing reasons, the Office has not met its burden of proving a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that this rejection be withdrawn.

III. Double Patenting Rejection

The Office rejected claims 21-22 under the nonstatutory obviousness-type double patenting doctrine as being unpatentable over: (a) claims 1-9 of U.S. Patent No. 6,774,122 and (b) claims 1-12 of U.S. Patent No. 7,456,160.

Because Applicants cancelled claims 21 and 22 in this Response, this rejection is now moot. Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not included with this Response to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 20, 2011

By: _____

Carlos M. Téllez
Reg. No. 48,638
(202) 408-4123

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
John R. Evans et al.	) Group Art Unit: 1628
Application No.: 12/285,887	) Examiner: HUI, San Ming R.
Filed: October 15, 2008	) Confirmation No.: 1199
For: FORMULATION	) **VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

A. Documents Listed in the Attached SB/08 Form

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(c), Applicants brings to the attention of the Examiner the documents on the attached listing. This Information Disclosure Statement is being filed after the events recited in Section 1.97(b) but, to the undersigned's knowledge, before the mailing date of either a Final action, Quayle action, or a Notice of Allowance. Under the provisions of 37 C.F.R. § 1.97(c), this Information Disclosure Statement is accompanied by a fee of $180.00 as specified by Section 1.17(p).

Applicants respectfully request that the Examiner consider the listed documents and indicate that they were considered by making appropriate notations on the attached form.

B. Teva's Paragraph IV Letter Dated November 25, 2009

The undersigned wishes to make of record the following information. Teva Parenteral Medicines, Inc., ("Teva") filed Abbreviated New Drug Application ("ANDA") No. 200479 with the FDA seeking approval of a generic 50 mg/mL Fulvestrant injection. In connection with ANDA No. 200479, Teva sent a letter to AstraZeneca Pharmaceuticals LP dated November 25, 2009, ("Teva's Letter") concerning U.S. Patent Nos. 6,774,122 and 7,456,160 ("the '122 and '160 patents").

The instant application claims the benefit of priority from each of the '122 and '160 patents. Teva's Letter alleges that the '122 and '160 patents are obvious in light of, *inter alia*, Howell *et al.* (cited in the Information Disclosure Statement filed on June 4, 2009) and McLeskey *et al.* (cited in this Information Disclosure Statement).

All documents cited in Teva's Letter are listed in the table below. To the extent Teva's Letter provided a pinpoint citation for any of the documents, the citation is also provided below. Otherwise, the phrase "generally" appears when Teva's Letter referred to the disclosure in the given document without a citation.

References cited in Teva's Paragraph IV Letter Dated November 25, 2009, Concerning AstraZeneca's U.S. Patent Nos. 6,774,122 and 7,456,160	
Reference	**Citation**
U.S. Patent No. 5,183,814 to Dukes et al., and its "European cognate," European Patent Application No. EP 0 346 014	Generally; Col. 3, l. 66 - Col. 4, l. 4; Col. 6, ll. 20-26; Col. 9, ll. 15-25; Example 3, col. 11, ll. 1-11

References cited in Teva's Paragraph IV Letter Dated November 25, 2009, Concerning AstraZeneca's U.S. Patent Nos. 6,774,122 and 7,456,160	
Reference	**Citation**
U.S. Patent No.4,659,516 to Bowler et al. (and European Patent Application No. EP 0 138 504, which was termed an "equivalent" of U.S. Patent No.4,659,516 in Teva's Letter)	Generally
European Patent Application No. EP 0 346 014, which was termed the "European cognate" of U.S. Patent No. 5,183,814 in Teva's Letter	Generally
Howell *et al.*, "Pharmacokinetics, Pharmacological, and Anti-tumour Effects of the Specific Anti-oestrogen ICI 182780 in Women with Advanced Breast Cancer," *Brit J. Cancer* 74:300-308 (1996).	Generally; 300; 301; 302; 303; 305 Figure 2;
McLeskey *et al.*, "Tamoxifen-Resistant Fibroblast Growth Factor-Transfected MCF-7 Cells are Cross-Resistant *In Vivo* to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors," *Clin. Cancer Res.* 4:697-711 (1998).	Generally; 698
Wakeling *et al.*, "A Potent Specific Pure Antiestrogen with Clinical. Potential," Cancer Res., 51:3867-73 (1991).	Generally; 3869
U.S. Patent No. 4,212,863	Col. 1, ll. 30-32
P.K. Gupta and GA. Brazeau (eds), *Injectable Drug Development:Techniques to Reduce Pain and Irritation*. Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999).	405 418

AstraZeneca Pharmaceuticals LP and other AstraZeneca related corporate entities brought suit against Teva and other Teva related corporate entities charging

them with infringement of the '122 and '160 patents. The suit was filed on January 7, 2010 in the U.S. District Court for the District of Delaware and was assigned Civil Action No. 10-18-JAP.

Subsequently, Teva withdrew ANDA No. 200479 and is no longer seeking approval of a generic 50 mg/mL Fulvestrant injection from the FDA. Civil Action No. 10-18-JAP was dismissed without prejudice on June 15, 2011.

Unless already of record, all documents cited in the preceding table are being submitted to the Office in the attached SB/08 form.

C. Documents from the prosecution of European Patent Applications member of the same family as the instant application

Applicants submitted documents from the opposition against European Patent Application No. 01900186.6 with the Information Disclosure Statement filed June 4, 2009. Applicants now supplement that submission with documents submitted after the June 4, 2009, Information Disclosure Statement. Applicants are also enclosing the search reports from European Patent Application Nos. 10180667.7 and 10180661.0. European Patent Application Nos. 01900186.6, 10180667.7, and 10180661.0 are European members of the same patent family as the instant application.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the documents listed in the attached SB/08 form or in the table above are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claims in the application and Applicant determines that the cited documents do not constitute "prior

art" under United States law, applicant reserves the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement not included herein, please charge the fee to Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 20, 2011

By: _____

Carlos M. Téllez
Reg. No. 48,638
(202) 408-4123

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	12/285,887
				Filing Date	October 15, 2008
				First Named Inventor	John R. EVANS
				Art Unit	1628
				Examiner Name	San Ming R. Hui
Sheet	1	of	1	Attorney Docket Number	11285.0056-00000

U.S. PATENTS AND PUBLISHED U.S. PATENT APPLICATIONS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Issue or Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		US-			
		US-			
		US-			
		US-			
		US-			

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation[6]

NONPATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	Translation[6]
	1	McLeskey et al., "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant *in vivo* to the antiestrogen ICI 182,780 and two aromatase inhibitors," Clin. Cancer Res., 4:697-711 (1998).	
	2	JRF Robertson, et al., "Fulvestrant: pharmacokinetics and pharmacology," British Journal of Cancer, 90(1):S7-S10 (2004).	
	3	John F. R. Robertson, "Fulvestrant (Faslodex®)--how to make a good drug better," The Oncologist, 12:774-784 (2007).	
	4	Search Report for European Patent Application No. 10180667.7 dated November 23, 2010.	
	5	Search Report for European Patent Application No. 10180661.0 dated January 19, 2011.	
	6	Documents from the Opposition against European Patent Application No. 01900186.6 from April 21, 2009 to September 7, 2009.	

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Patent Application Fee Transmittal

Application Number:	12285887
Filing Date:	15-Oct-2008
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Filer:	Carlos M. Tellez/Delia Herring
Attorney Docket Number:	11285.0056-00000

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1290**

Electronic Acknowledgement Receipt

EFS ID:	10343633
Application Number:	12285887
International Application Number:	
Confirmation Number:	1199
Title of Invention:	Formulation
First Named Inventor/Applicant Name:	John R. Evans
Customer Number:	22852
Filer:	Carlos M. Tellez
Filer Authorized By:	
Attorney Docket Number:	11285.0056-00000
Receipt Date:	20-JUN-2011
Filing Date:	15-OCT-2008
Time Stamp:	16:59:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1290
RAM confirmation Number	4028
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		11285-0056-00000--20-JUN-2011--ResponseandAmendment.pdf	587464 f0c060149d0e3c9cfe78972c101304eb349e299b	yes	17

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	8
	Applicant Arguments/Remarks Made in an Amendment	9	17

Warnings:

Information:

2		11285-0056-00000--20-JUN-2011--IDSandSB08.pdf	73727 27bc537a476efc3075103da02bd9fdf7b2751a2f	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	5
	Information Disclosure Statement (IDS) Form (SB08)	6	6

Warnings:

Information:

3	Non Patent Literature	11285-0056-00000--20-JUN-2011--MCLESKEY.pdf	552191 19a6a50aac4a78d8423d3acab80cb2225de83120	no	15

Warnings:

Information:

4	Non Patent Literature	11285-0056-00000--20-JUN-2011--JFRRobertsonFulvestraint.pdf	118217 85e15a34de0ba428157506d8e148b124bce26f17	no	4

Warnings:

Information:

5	Non Patent Literature	11285-0056-00000--20-JUN-2011--JohnFRRobertson.pdf	291690 41898efd490c024a52c360ac37be99c00825e857	no	12

Warnings:

Information:

6	Foreign Reference	11285-0056-00000--20-JUN-2011--ISR10180667-7.pdf	65906 10fa5d3615cf47dba314a172adac66c1aa834914	no	5

Warnings:

Information:					
7	Foreign Reference	11285-0056-00000--20-JUN-2011--ISR10180661-0.pdf	66093 549156ea24a6e5820e5b114f514966558a01342b	no	5
Warnings:					
Information:					
8	Non Patent Literature	11285-0056-00000--20-JUN-2011--DocumentsfromOpposition.pdf	697437 fcc44c176cbe2b76f5ea85a1b1162d8d5e300552	no	51
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	31886 ff9996e9130d928a675262ef7a75a7e64bc11611	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2484611	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/285,887	Filing Date 10/15/2008	☒ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/20/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 23	= 7	X $ =		OR	X $52=	364
	Independent (37 CFR 1.16(h))	* 8	Minus	***3	= 5	X $ =		OR	X $220=	1100
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**1464**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/NICHELE PETERSON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Document code: WFEE

United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/285,887	10/15/2008	John R. Evans	11285.0056-00000	1199

22852 7590 09/16/2011

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
09/16/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/285,887	EVANS ET AL.	
	Examiner	Art Unit	
	SAN-MING HUI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *24-53* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *24-53* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is a continuation of US 10/872,784, filed 6/22/2004, now patent 7,456,160, which is a continuation of US 09/756,291, filed 1/9/2001, now patent 6,774,122. The instant application also claims the benefit of UNITED KINGDOM 0000313.7, filed 01/10/2000 and UNITED KINGDOM 0008837.7, filed 04/12/2000.

Applicant's amendments filed 6/20/2011 have been entered. Claims 24-53 are pending.

The outstanding rejection under 35 USC 103(a) is withdrawn due to the cancellation of the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,774,122 (‘122). Although the conflicting claims are not identical, they are not patentably distinct from each other because '122 teaches the method of treating hormonal dependent benign or malignant disease of reproductive tract by employing the herein claimed composition. The ratio of the solvents and the excipients are within the range taught in '122. The optimization of result effect parameters (e.g., dosing regimen, weight ratio of the actives and the excipients) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition

in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 24-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 7,456,160 ('160). Although the conflicting claims are not identical, they are not patentably distinct from each other because '160 teaches the method of treating hormonal dependent benign or malignant disease of reproductive tract by employing the herein claimed composition. The ratio of the solvents and the excipients are within the range taught in '160. The optimization of result effect parameters (e.g., dosing regimen, weight ratio of the actives and the excipients) is obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKeskey et al., from IDS filed 6/20/2011 in view of Dukes (EP 0 346 014), Osborne et al., Journal of National Cancer Institute, 1995;87(20):746-750, and the abstract of Wakeling et al., The Journal of Steroid Biochemistry and Molecular Biology, 1992;43(1-3):173-177.

McKeskey et al. teaches a studies employing subcutaneous injection of fulvestrant to nude mice. The fulvestrant formulation contains 50mg/ml in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol brought to volume with castor oil (see page 698, col. 2, Drugs section).

McKeskey et al. does not expressly teach the use of fulvestrant in treating hormonal dependent diseases of breast. It does not expressly teach the dosing regimen to be once a month, intramuscular administration, or the volume administered. McKeskey et al. does not expressly teach the herein claimed serum concentration of fulvestrant.

Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen

agent, including fulvestrant, via intramuscular route of administration may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, line 20-24).

Osborne et al. teaches fulvestrant as useful in treating human breast cancer (See pages 747- 748, Result Section).

Wakeling et al. teaches the administration of fulvestrant (ICI 182780) demonstrating the antiestrogenic effect for over a 1 month period (see the abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ fulvestrant in McKeskey's, in the herein claimed dosing regimen and dosage, for treating hormonal dependent diseases such as breast cancer and postmenopausal symptoms.

One of ordinary skill in the art would have been motivated to employ fulvestrant in McKeskey's, in the herein claimed dosing regimen and dosage, for treating hormonal dependent diseases such as breast cancer and postmenopausal symptoms. It is known in the art that fulvestrant as being useful in treating hormonal dependent disease. It is also known in the art that fulvestrant can be administered intramuscularly and its antitumor effect can last for more than 1 month. Employing McKeskey's formulation of fulvestrant for intramuscular administration would be seen as obvious since administering a relative large volume of fulvestrant (5ml) would not be appropriate for subcutaneous administration. The examiner notes that in McKeskey's study, only 0.1ml was injected via subcutaneous administration. Furthermore, the optimization of result effect parameters (e.g., dosing regimen, weight ratio of the actives and the excipients) is

obvious as being within the skill of the artisan. The optimization of known effective amounts of known active agents to be administered, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). It is also noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The examiner notes that the herein claimed serum concentration is considered to be an inherent effect of the formulation of fulvestrant.

Response to Arguments

Applicant's arguments with respect to claims 24-53 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN-MING HUI whose telephone number is (571)272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui

Primary Examiner
Art Unit 1628

/San-ming Hui/
Primary Examiner, Art Unit 1628

Notice of References Cited	Application/Control No. 12/285,887	Applicant(s)/Patent Under Reexamination EVANS ET AL.	
	Examiner SAN-MING HUI	Art Unit 1628	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	The abstract of Wakeling et al., The Journal of Steroid Biochemistry and Molecular Biology, 1992;43:1-3:173-177
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12285887	EVANS ET AL.
	Examiner	Art Unit
	San-ming Hui	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/19/2010	09/06/2011							
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
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	29		✓							
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	31		✓							
	32		✓							
	33		✓							
	34		✓							
	35		✓							
	36		✓							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12285887	EVANS ET AL.
	Examiner	**Art Unit**
	San-ming Hui	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/19/2010	09/06/2011							
	37		✓							
	38		✓							
	39		✓							
	40		✓							
	41		✓							
	42		✓							
	43		✓							
	44		✓							
	45		✓							
	46		✓							
	47		✓							
	48		✓							
	49		✓							
	50		✓							
	51		✓							
	52		✓							
	53		✓							

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	82307	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L2	387	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L3	2488	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L4	3	"4659516".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L5	7	"346014".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L6	15161	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L7	1829323	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L8	7808	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L9	4	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (estrogen or estradiol or estrone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L10	7	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L11	13	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L12	1810	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58

L13	2	"6774122".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L14	951	514/177.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L15	1378	514/178.ccls.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L16	2093489	castor oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L17	82307	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L18	387	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L19	2488	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L20	15161	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L21	1829323	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L22	7808	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L23	7	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (testosterone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L24	13	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L25	1810	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L26	82307	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L27	4762	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT;	OR	ON	2011/09/06 18:58

			IBM_TDB			
L28	2718	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L29	1411	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L30	3	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L31	3264	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L32	3264	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L33	82307	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L34	387	fulvestrant and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L35	2488	oil and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L36	3	"4659516".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L37	7	"346014".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L38	15161	(benzyl adj benzoate) or (phenylmethyl adj benzoate)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L39	1829323	solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L40	7808	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L41	4	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (estrogen or estradiol or estrone)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L42	7	(((benzyl adj benzoate) or	US-PGPUB;	OR	ON	2011/09/06

		(phenylmethyl adj benzoate)) same solvent) same (testosterone)	USPAT; EPO; JPO; DERWENT; IBM_TDB			18:58
L43	13	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) same (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L44	1810	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same solvent) and (steroid)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L45	82307	castor adj oil	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L46	4762	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) and (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L47	2718	((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L48	1411	(((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L49	3	((((benzyl adj benzoate) or (phenylmethyl adj benzoate)) same (castor adj oil)) same solvent) same steroid	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L50	3264	fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L51	90122	breast adj cancer	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L52	2211	breast adj cancer and fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L53	342	breast adj cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L54	1407	cancer same fulvestrant	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L55	2	"7456160".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58
L56	2	"6,774,122".pn.	US-PGPUB; USPAT; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/09/06 18:58

EAST Search History (Interference)

<This search history is empty>

9/6/2011 7:04:28 PM
C:\Users\shui\Documents\EAST\Workspaces\12-285887.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12285887	EVANS ET AL.
	Examiner	**Art Unit**
	San-ming Hui	1628

SEARCHED			
Class	**Subclass**	**Date**	**Examiner**
514	177, 178	12/19/10	SH
514	177, 178	9/6/11	SH

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
EAST and inventor search in PALM	12/19/10	SH
update search in EAST and inventor search in PALM	9/6/11	SH

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number: **12/285,887**	Confirmation Number: 1199
Filing Date: October 15, 2008	
First Named Inventor: John E. EVANS	
Group Art Unit: 1628	
Examiner: HUI, San Ming R.	
Attorney Docket Number: 11285.0056-00000	

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 C.F.R. § 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application.

1. **Submission required under 37 C.F.R. § 1.114: Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment.**

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on_____.

      ii. ☐ Other _____

   b. ☐ **DO NOT ENTER** the amendment(s) previously filed on_____. An alternate submission is attached.

   c. ☒ Enclosed submission:

      i. ☒ Amendment/Reply

      ii. ☒ Affidavit(s)/Declaration(s)

      iii. ☒ Information Disclosure Statement

      iv. ☒ Other Terminal Disclaimer

2. Miscellaneous

   a. ☐ Suspension of action on the above-mentioned application is requested under 37 C.F.R. § 1.103(c) for a period of ____ months. (Period of suspension shall not exceed 3 months; fee under 37 C.F.R. § 1.17(i) required.)

   b. ☐ Other _____

3. Fees

   a. ☒ The filing fee is calculated as follows:

      i. ☒ $930.00 RCE fee required under 37 C.F.R. § 1.17(e)

      ii. ☒ Petition for extension of time for (one (1) Months) **$150.00**

      iii. ☒ Other Terminal Disclaimer **($160.00)**

   b. ☒ Payment in the amount of **$1,240.00** enclosed.

   c. ☒ The Commissioner is authorized to charge any deficiencies in the filing fees, or credit any overpayments to Deposit Account No. 06-0916.

Signature of Applicant, Attorney, or Agent Required

Name: Carlos M. Téllez	(202) 408-4000	Reg. No.: 48,638
Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.		
Signature: /Carlos M. Téllez/		Date: January 17, 2012

Certificate of Mailing or Transmission

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner for Patents, MAIL STOP RCE, P.O. Box 1450, Alexandria, VA. 22313-1450, or facsimile transmitted to the U.S. Patent and Trademark Office on:

Name:	
Signature:	Date:

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
John R. Evans et al.	)	Group Art Unit: 1628
	)	
Application No.: 12/285,887	)	Examiner: HUI, San Ming R.
	)	
Filed: October 15, 2008	)	Confirmation No.: 1199
	)	
For: FORMULATION	)	**VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(b)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicant brings to the attention of the Examiner the listed documents on the attached listing. This Information Disclosure Statement is being filed before the mailing date of a first Office Action after the filing of a Request for Continued Examination in the above-referenced application.

Copies of the listed foreign and non-patent literature documents are attached. Copies of the U.S. patent publications are not enclosed.

Documents from the prosecution of European Patent Applications members of the same family as the instant application

Applicants had submitted documents in previous Information Disclosure Statements from the prosecution histories of European Patent Application Nos. 01900186.6 (EP 1 250 138), 10180667.7 (EP 2 266 573), and 10180661.0 (EP 2 286 818), which are European members of the same patent family as the instant application. Applicants now supplement those submissions with documents made of

record in those European applications after the previous Information Disclosure Statement was filed.

Applicants respectfully request that the Examiner consider the listed documents and indicate they were considered by making appropriate notations on the attached form.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claims in the application and Applicants determine that the cited documents do not constitute "prior art" under United States law, applicants reserve the right to present to the office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 17, 2012

By: _____

Carlos M. Téllez
Reg. No. 48,638
(202) 408-4123

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
John R. Evans et al.	)	Group Art Unit: 1628
	)	
Application No.: 12/285,887	)	Examiner: HUI, San Ming R.
	)	
Filed: October 15, 2008	)	Confirmation No.: 1199
	)	
For: FORMULATION	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TERMINAL DISCLAIMER

Assignee, AstraZeneca AB, duly organized under the laws of Sweden and having its principal place of business at S-151 85 Sodertalje, Sweden, represents that is the assignee of the entire right, title, and interest in and to the above-identified application, Application No. 12/285,887 ("the '887 application"), filed on October 15, 2008, entitled "Formulation," in the names of John R. EVANS, and Rosalind U. GRUDY, as indicated by the assignment duly recorded in the United States Patent and Trademark Office for U.S. Application No. 10/872,784 ("the '784 application"), now U.S. Patent No. 7,456,160 (the '887 application being a Continuation of the '784 application) at Reel 015906, Frame 0402 on October 14, 2004.

Assignee, AstraZeneca AB, further represents that it is the assignee of the entire right, title, and interest in and to U.S. Patent Nos. 6,774,122, and 7,456,160 as indicated by the assignments duly recorded in the United States Patent and Trademark Office at

Reel 011635, Frame 0063 on March 27, 2001, and Reel 015906, Frame 0402 on October 18, 2004, respectively.

To obviate a double patenting rejection, Assignee hereby disclaims, except as provided below, the terminal part of the statutory term of any patents granted on the instant application that would extend beyond the expiration date of the full statutory term, as presently shortened by any terminal disclaimer, of prior U.S. Patent Nos. 7,456,160 and 6,774,122. Assignee hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, Assignee does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patents, as presently shortened by any terminal disclaimer, in the event that the prior patent later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or in part, is terminally disclaimed under 37 C.F.R. § 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated before the expiration of its full statutory term as presently shortened by any terminal disclaimer.

In accordance with the fee schedule in 37 C.F.R. § 1.20(d), the required fee of $160.00 is being filed with this disclaimer.

If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to Deposit Account No. 06-0916.

The undersigned is authorized to act on behalf of assignee AstraZeneca AB.

I hereby declare that all statements made of my own knowledge and belief are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: 12th January 2012

By: _____
Signature
Name: ALLEN FRANK GILES
Title: AUTHORISED SIGNATORY
Assignee: AstraZeneca AB

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
John R. Evans et al.	)	Group Art Unit: 1628
	)	
Application No.: 12/285,887	)	Examiner: HUI, San Ming R.
	)	
Filed: October 15, 2008	)	Confirmation No.: 1199
	)	
For: FORMULATION	)	**Mail Stop RCE**
	)	
	)	**VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE TO OFFICE ACTION, SUBMISSION UNDER 37 C.F.R. § 1.114, AND PETITION FOR EXTENSION OF TIME

In reply to the Final Office Action mailed September 16, 2011 ("Office Action"), Applicants respectfully request reconsideration of the claimed invention in view of the following amendments and remarks. This paper fulfills the requirements of a submission under 37 C.F.R. § 1.114, and is filed together with a Request for Continued Examination (RCE).

Applicants hereby petition for a one-month extension of time to respond to the Office Action, extending the period for response to January 16, 2012. The requisite extension-of-time fee is being paid concurrently with this filing.

Amendments to the Claims are reflected in the listing of claims, which starts on page 2 of this paper. **Remarks** follow the amendment sections of this paper and start on page 7.

REMARKS

I. Status of the claims and amendments

Upon entry of the instant amendments, claims 24, 26, 27, 29, 30, 32, 34-36, 38, 39, 41, 42, 44, 46, 47, and 54-57 will be pending in this application. Claims 25, 28, 31, 33, 37, 40, 43, 45, and 48-53 are cancelled in this Response without prejudice or disclaimer. New claims 54-57 are added in this Response and find support, for example, in the specification at ¶ [0053].[1]

Applicants amended claim 24 to recite a formulation comprising "about 50 mgml-1 of fulvestrant; about 10% w/v of ethanol; about 10% w/v of benzyl alcohol; and about 15% w/v of benzyl benzoate." Support for this amendment can be found, for example, in the specification at ¶¶ [0072]-[0075]. Applicants also amended claim 24 to recite that the method achieves a therapeutically significant blood plasma fulvestrant concentration "for at least four weeks." Support for this amendment can be found, for example, in the specification at ¶ [0052]. Applicants amended claim 36 in a similar manner to claim 24, with support in the same portions of the specification as the amendments to claim 24 mentioned above. Applicants amended claims 32, 34, 44, and 46 to change their dependency because the claim from which each depended has been cancelled in this Response. None of the claim amendments introduce new matter.

Claims 24, 26, 27, 29, 30, 32, 34, 35, 54 and 55 are directed to methods for treating a hormonal dependent benign or malignant disease of the breast or

[1] Unless otherwise specified, all citations to the instant specification refer to the pagination in the published application, US 2010/0152149.

reproductive tract comprising administering intramuscularly to a human in need of such treatment a formulation *comprising* various components. Claims 36, 38, 39, 41, 42, 44, 46, 47, 56, and 57 are identical to claims 24, 26, 27, 29, 30, 32, 34, 35, 54 and 55 except that the phrase "formulation *consisting essentially of*" replaces the phrase "formulation *comprising*" the various components.

II. Statement of Substance of Interview under 37 C.F.R. § 1.133(b)

Applicants would like to thank Examiner San Ming Hui for granting a personal interview to Applicants on August 4, 2011. Applicants present this Statement of Substance of Interview in connection with that interview conducted between Examiner San Ming Hui, the undersigned, Dr. Paul R. Gellert (AstraZeneca Pharmaceuticals), and Mr. Allen F. Giles (AstraZeneca Pharmaceuticals).

During the interview, the undersigned and the Examiner discussed the then pending claims 24-53 and the disclosures of the following references: a) Howell et al., "Pharmacokinetics, Pharmacological, and Anti-tumour Effects of the Specific Anti-Estrogen ICI 182780 in Women with Advanced Breast Cancer," *Brit J. Cancer* 74:300-308 (1996), b) European Patent Application No. EP 0 346 014, and McLeskey et al., "Tamoxifen-Resistant Fibroblast Growth Factor-Transfected MCF-7 Cells are Cross-Resistant In Vivo to the Antiestrogen ICI 182,780 and Two Aromatase Inhibitors," *Clin. Cancer Res*. 4:697-711 (1998).

At the interview, the undersigned also mentioned the status of the lawsuit between AstraZeneca Pharmaceuticals and Teva Parenteral Medicines concerning a generic product containing 50 mg/ml of fulvestrant, which was also mentioned in the Information Disclosure Statement filed on June 20 , 2011.

No agreement was reached and the Examiner indicated he would consider the information presented at the interview in the preparation of the next Office Action.

III. Double Patenting Rejection

The Office rejected claims 24-53 under the nonstatutory obviousness-type double patenting doctrine as being unpatentable over: (a) claims 1-9 of U.S. Patent No. 6,774,122 ("the '122 patent") and (b) claims 1-12 of U.S. Patent No. 7,456,160 ("the '160 patent").

With the sole purpose of expediting prosecution, Applicants submit a Terminal Disclaimer concurrently with this Response, which shows common ownership of the instant application and the '122 and '160 patents and should obviate this rejection. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The filing of the Terminal Disclaimer is not an admission of the alleged obviousness of the instant claims in light of the claims in the '122 and '160 patents. *See, e.g.*, M.P.E.P. § 804.02.II; *Quad Environmental Technologies, Corp. v. Union Sanitary District*, 946 F.2d 870, 874 (Fed. Cir. 1991).

IV. Errors in the specification

Applicants would like to remind the Office of certain errors appearing in the instant specification. Applicants mentioned those errors in the Declaration Under 35 U.S.C §1.132 of Dr. Paul Gellert filed on August 2008 ("the Gellert Declaration"), in the parent application (Application No. 10/872,784). Applicants listed the Gellert Declaration in an Information Disclosure Statement being filed concurrently with this Response.

V. Rejections under 35 U.S.C. 103(a)

The Office rejected claims 24-53 under 35 U.S.C. 103(a) as being unpatentable over McLeskey et al., *Clinical Cancel Research* 4:697-711 (1998) ("*McLeskey*"); in view of European Patent Specification No. EP 0 346 014, which names Michael Dukes as inventor ("*Dukes*"); Osborne et al., *Journal of National Cancer Institute*, 87(20):746-750 (1995) ("*Osborne*"); and the abstract of Wakeling et al., "ICI 182,780, *J. Steroid Biochemistry and Molecular Biology*, 43(1-3):173-177 (1992) ("*Wakeling*"). Office Action at 5.

According to the Office, *McLeskey* teaches "a stud[y] employing subcutaneous injection of fulvestrant to nude mice" and a "fulvestrant formulation contain[ing] 50mg/ml in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol brought to volume with castor oil." *Id.* The Office acknowledges that *McLeskey* does not expressly teach "the use of fulvestrant in treating hormonal dependent diseases of breast", "the dosing regimen to be once a month, intramuscular administration", "the volume administered", or "the herein claimed serum concentration of fulvestrant." *Id.*

In the Office's view, *Dukes* teaches that "antiestrogen agent[s], including fulvestrant, via intramuscular route of administration may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol." *Id.* at 5-6.

The Office cites *Osborne* as teaching that fulvestrant is "useful in treating human breast cancer" (*id.* at 6) and *Wakeling* as teaching that "the administration of fulvestrant (ICI 182780) demonstrat[es] the antiestrogenic effect for over a 1 month period." *Id.*

According to the Office "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to employ fulvestrant in [*McLeskey*], in the

herein claimed dosing regimen and dosage, for treating hormonal dependent diseases such as breast cancer and postmenopausal symptoms" because it is "known in the art that fulvestrant can be administered intramuscularly and its antitumor effect can last for more than 1 month." *Id.*

The Office argues that "[e]mploying *McLeskey's* formulation of fulvestrant for intramuscular administration would be seen as obvious since administering a relative large volume of fulvestrant (5ml) would not be appropriate for subcutaneous administration." *Id.* The Office further argues that "the optimization of result effect[ive] parameters (e.g., dosing regimen, weight ratio of the actives and the excipients) is obvious as being within the skill of the artisan." *Id.* Applicants respectfully traverse this rejection.

A. Declaration of Dr. Ronald J. Sawchuk

In support of Applicants' statements regarding the state of the art and how one of ordinary skill in the art would have understood the references cited in the Office Action prior to the earliest priority date for the instant application (January 10, 2000), Applicants submit concurrently with this Response a declaration by Dr. Ronald J. Sawchuk ("Sawchuk Decl.").

B. The Office has not made the necessary factual findings to support a conclusion of obviousness

Applicants understand that the Office's rejection is based on at least the following two implicit assumptions: 1) that a person of ordinary skill in the art ("POSITA") would have chosen the fulvestrant composition disclosed in *McLeskey*, from among all other known compositions in which fulvestrant had been dissolved, for the development of a

method of treating the diseases recited in the claims, and 2) that the POSITA would have had a reasonable expectation that such a composition would have been successful in those methods. Applicants respectfully submit that the Office has not provided support for those assumptions.

Applicants respectfully remind the Office that the focus in an obviousness rejection is not on what one of ordinary skill in the art *could have done*, but rather "on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person *would have reasonably expected to have been able to do* in view of that knowledge. M.P.E.P. § 2141.II (emphasis added). Thus, two of the relevant questions in this rejection are: (1) whether the knowledge in the art would have suggested to a POSITA that *McLeskey's* composition had some advantages over other known fulvestrant compositions such that it would have been selected for the development of a method of human treatment, and (2) even assuming that a POSITA would have selected the fulvestrant *McLeskey's* composition for the development of a method of treatment, whether in light of the knowledge in the art prior to January 10, 2000, one of ordinary skill in the art would have expected that the fulvestrant *McLeskey* composition cited by the Office would have been successful in a method of treating as recited in the instant claims.

Specifically, regarding the second question, even after *KSR*, an obviousness rejection in which the Office argues that the claimed invention would have been the result of a combination of references requires that the Office show that one of ordinary skill in the art would have had a reasonable expectation of success when combining the references. M.P.E.P. § 2143.02; *see also* M.P.E.P. § 2143.A (addressing the

requirements for a "combination of prior art elements" rationale). As will be explained below, a critical review and analysis of the state of the art at the time the instant application was filed leads to the conclusion that no such expectation existed.

Applicants will explain and discuss below the following *independent* reasons supporting withdrawal of the instant obviousness rejection:

(1) *McLeskey* would not have suggested to a POSITA the specific %w/v composition recited in the claims;

(2) None of the cited references would have provided a POSITA with information to select the fulvestrant composition disclosed in *McLeskey* over other known fulvestrant compositions;

(3) The POSITA would not have had a reasonable expectation that the *McLeskey* composition would have been successful in such a method. Applicants present two independent arguments to support a lack of expectation of success:

   a. One of ordinary skill in the art would have understood that results from subcutaneous administration, such as those in *McLeskey*, cannot be extrapolated to intramuscular administration and, thus, a POSITA would not have a had an expectation as to whether the fulvestrant composition from *McLeskey* would have been effective for intramuscular delivery of fulvestrant.

   b. Numerous variables affect the efficacy of an intramuscular formulation, among them the identity and proportion of each of its cosolvents, and a POSITA understands that the resulting variability precludes a POSITA from having an expectation a priori that a given formulation would be

successful in a given method of treatment until actual suitable in vivo experiments are performed.

1. *Independent Reason 1. McLeskey* would not have suggested to a POSITA the specific %w/v composition recited in the claims

McLeskey discloses two fulvestrant compositions. One composition was prepared by dissolving powdered drug in 100% ethanol and then spiking it into warmed peanut oil to give a final concentration of 50 mg/ml ("the *McLeskey* peanut oil composition"). *McLeskey* at 698, col. 2, under "Drugs"; Sawchuk Decl. at ¶ 16. The second composition is a 50 mg/ml fulvestrant composition "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor-oil" ("the *McLeskey* castor oil composition"). *Id.* The Office only refers to the *McLeskey* castor oil composition in the Office Action. Office Action at 5.

McLeskey does not specify whether the percentages in the *McLeskey* castor oil composition are in weight/volume units (%w/v, as recited in the instant claims) or in volume/volume units (%v/v). Sawchuk Decl. at ¶ 16. Dr. Sawchuk states that "[i]In a liquid composition, when a solute or cosolvent is a liquid, it is often convenient to express its concentration as a volume percent, i.e., % v/v." *Id.* at ¶ 17.

Dr. Sawchuk provides various examples of references in which the concentration of liquid components in a composition is reported in terms of %v/v values, whereas the concentration of solid solutes is reported in terms of %w/v. *Id.* at ¶¶ 18-20.
Dr. Sawchuk concludes that "[b]ecause all of the components of the vehicle disclosed in *McLeskey* are liquids, one of ordinary skill in the art would have concluded that the

composition was described in terms of volume/volume percent units (% v/v)." *Id.* at ¶ 21.

Based on that information, Dr. Sawchuk states that "one of ordinary skill in the art would have concluded that the *McLeskey* castor oil composition on page 698 was reported in % v/v units and referred to a composition containing 10% **v**/v ethanol, 15% **v**/v benzyl benzoate, and 10% **v**/v benzyl alcohol in a castor oil vehicle. *Id.* at ¶ 22. This composition *is different* from a composition containing 10% **w**/v ethanol, 15% **w**/v benzyl benzoate, and 10% **w**/v benzyl alcohol in a castor oil vehicle. *Id.* The units of the fulvestrant composition recited in the instant claims are %**w**/v.

Dr. Sawchuk converted the %v/v values that *McLeskey* would have suggested to a POSITA into %w/v values, which would allow a direct comparison between the *McLeskey* castor oil composition and the composition recited in the instant claims. *Id.* at ¶¶ 23-27. Table 1 below shows the results of the calculation, with Column E having the final concentration values in %w/v units for each component in the *McLeskey* castor oil composition. *Id.* at ¶ 27.

Table 1. Information for 100 ml of the fulvestrant *McLeskey* castor oil composition

	A	B	C	D	E
Component	**% v/v**	**Volume (ml)**	**Density (g/ml)**	**Weight (g)**	**% w/v**
Ethanol	10	10	0.808	8.08	8.1
Benzyl Benzoate	15	15	1.118	16.77	16.8
Benzyl Alcohol	10	10	1.04156	10.42	10.4

According to Dr. Sawchuk, a POSITA "reading *McLeskey* would have concluded that *McLeskey* described a composition containing about **8.1% w/v** ethanol, about

10.4% w/v benzyl alcohol, and about **16.8 % w/v** benzyl benzoate in a castor oil vehicle." *Id.* at ¶ 29. Therefore, *McLeskey would not have suggested the fulvestrant composition recited in the claims comprising about **10% w/v** of ethanol; about **10% w/v** of benzyl alcohol; and about **15% w/v** of benzyl benzoate.*

In Dr. Sawchuk's opinion, none of the references cited in the Office Action contain any disclosure "that would have suggested to one of ordinary skill in the art the modification of a composition containing about 8.1% w/v ethanol, about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol (i.e., the *McLeskey* castor oil composition) in an attempt to produce a composition as recited in the claims containing about 10% w/v ethanol, about 15% w/v benzyl benzoate, and about 10% v/v benzyl alcohol". *Id.* at ¶ 30.

For at least this reason, the cited references, either alone or in combination, fail to meet all of the limitations of the claims, and Applicants respectfully request that this rejection be withdrawn.

2. ***Independent Reason 2.*** **The Office has not shown that a POSITA would have selected the *McLeskey* castor oil composition for the development of a method of treating involving intramuscular administration as instantly claimed**

Applicants remind the Office that "[o]bviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Laboratories, Inc. v. Apotex, Inc.*, No. 2010-1006, slip op. at 13 (Fed. Cir. Aug. 25, 2011) (internal citations omitted). Indeed, the Federal Circuit explained that:

> [O]bviousness requires the additional showing that a person of ordinary skill at the time of the invention *would have selected and combined those prior art elements* in the normal course of research and development to yield the claimed invention.

Id. (internal citations omitted, italics added). Thus, in the instant rejection, the Office needs to identify reasons why a POSITA would have: a) selected and then b) combined the elements the Office argues are disclosed in the cited references. For example, the Office needs to explain why a POSITA would have selected the *McLeskey* castor oil composition (comprising ethanol, benzyl alcohol, and benzyl benzoate), from among the known fulvestrant formulations at the time of filing, to develop a method of treatment as instantly claimed.

Dr. Sawchuk explains that *McLeskey* provides no information that would have suggested to a POSITA the desirability of any of its two fulvestrant compositions over other known fulvestrant formulations. Sawchuk Decl. at ¶ 31. For example, Dr. Sawchuk points out that antitumor treatment with fulvestrant was ineffective in the *McLeskey* experiments. *Id.* at ¶ 33. In addition, with respect to the two formulations disclosed in *McLeskey*, Dr. Sawchuk highlights that *McLeskey* "did not provide any experimental data that would have allowed one of ordinary skill in the art to compare any aspect of the performance of the two fulvestrant compositions for the treatment of cancerous tumors." *Id.* at ¶ 31.

Therefore, in Dr. Sawchuk's opinion, "because of the lack of fulvestrant efficacy and the absence of pharmacokinetic data in *McLeske*y, one of ordinary skill in the art would have been unable to conclude whether either of the two fulvestrant *McLeskey* compositions (peanut oil or castor oil) was able to deliver a dose of fulvestrant that had

an antitumor therapeutic effect in the mice when administered subcutaneously." *Id.* at ¶ 35.

In light of those circumstances, Dr. Sawchuk concludes that "*McLeskey* provides no information that would have led one of ordinary skill in the art to have a preference for either the peanut oil or the castor oil fulvestrant compositions over the other one, or even a preference for one of the two *McLeskey* fulvestrant compositions over other fulvestrant compositions known in the art prior to January 10, 2000." *Id.* at ¶ 36.

Regarding fulvestrant compositions known in the art different from the *McLeskey* castor oil composition, Dr. Sawchuk lists various compositions disclosed in the references cited by the Office. *Id.* at ¶¶ 37-39. Among those formulations, Dr. Sawchuk mentions fulvestrant in an oil suspension (*Wakeling*), fulvestrant in a castor oil composition (*Osborne*), fulvestrant in a mixture of propylene glycol:ethanol:water:poloxamer 407 (*Dukes*), and fulvestrant in 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml (*Dukes*), in addition to the peanut oil fulvestrant composition from *McLeskey*. Sawchuk Decl. at ¶ 37-39.

Therefore, Dr. Sawchuk concludes, "one of ordinary skill in the art had other choices besides the *McLeskey* castor oil composition with respect to potential fulvestrant formulations that could have been further investigated for the development of a method of treating humans with intramuscular fulvestrant." *Id.* at ¶ 40. However, in Dr. Sawchuk' opinion, "none of the references cited in the Office Action provides any information that would have guided one of ordinary skill in the art to select the *McLeskey* castor oil composition, over any of the other fulvestrant compositions

mentioned above," for the potential development of a method of treatment as recited in the instant claims. *Id.*

In this regard, the Federal Circuit has explained that:

> When a field is unreduced by direction of the prior art, and when prior art gives no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, an invention is not obvious to try.

Unigene, slip op. at 15 (internal citation omitted).

In this case, the Office has not explained how the cited art directs a POSITA to select the *McLeskey* castor oil composition from among all other known fulvestrant compositions to develop a method as claimed. Indeed, according to Dr. Sawchuk, "none of the references cited by the Examiner provides any guidance as to the relevant factors to consider when selecting a formulation for the potential development of a method of treatment as recited in the instant claims." Sawchuk Decl. at ¶ 41.

Nonetheless, in Dr. Sawchuk's opinion, and judging solely on the basis of efficacy, "the *McLeskey* castor oil composition would have been among the least favored compositions to select for further development from among the fulvestrant compositions discussed above because one of ordinary skill in the art would not have been able to conclude from the information in *McLeskey* whether fulvestrant, using that composition, was sufficiently bioavailable to have an antitumor effect." *Id.* Rather, according to Dr. Sawchuk and based on only efficacy, "the fulvestrant oil suspension from *Wakeling* would have been among the most favored formulations to select for further development from among those discussed above because at least that

formulation, when given as a single injection, showed a therapeutic antitumor effect in mice for over a one-month period." *Id.*

Accordingly, at least because the Office has failed to explain why a POSITA would have selected the *McLeskey* castor oil composition from among those fulvestrant compositions known in the art at the time of filing to develop a method of treatment as claimed, the Office has not made a prima facie case of obviousness. Thus, Applicants respectfully request that this rejection be withdrawn.

3. One of ordinary skill in the art would not have had an expectation that the formulation disclosed in *McLeskey*, administered subcutaneously to mice, would have been successful for intramuscular administration as instantly recited

The POSITA would not have had a reasonable expectation that the *McLeskey* castor oil composition would have been effective to administer fulvestrant intramuscularly to achieve a therapeutic effect for at least four weeks, as instantly recited. Two independent reasons are set forth below supporting a lack of expectation of success for the combination of the references cited by the Office.

a) *Independent Reason 3.* A POSITA would not have had an expectation that the results from subcutaneous injection in *McLeskey* would have been applicable to the intramuscular administration of fulvestrant

One of ordinary skill in the art would have understood that results from subcutaneous administration, such as those reported in *McLeskey*, cannot be extrapolated to intramuscular administration. Sawchuk Decl. at ¶ 42. In Dr. Sawchuk's view, "one of ordinary skill in the art would not have had an expectation as to whether the *McLeskey* castor oil composition would have had a therapeutic effect when

administered intramuscularly before actually performing suitable in vivo experiments." *Id.*

Dr. Sawchuk cites a few examples in which comparison of the results from subcutaneous administration yielded significant differences with respect to those from intramuscular administration. For example, a study of administration of probenecid in ewes showed that administration of the same dose of probenecid, a drug which may be used to prolong the half-life of some antibiotics in animals, resulted in significant differences in absorption and bioavailability of the drug when administered subcutaneously or intramuscularly. Guerrini V.H., Filippich L.J., English P.B., Schneider J., Cao G.R. and Bourne D.W.A., "Pharmacokinetics of probenecid in sheep", *J Vet Pharmacol Ther.* 8(2):128-35 (1985) ("*Guerrini*"); Sawchuk Decl. at ¶ 44.

Dr. Sawchuk comments that in *Guerrini* the intramuscular dose was absorbed more rapidly and more completely than the subcutaneous dose, whereas the subcutaneous administration resulted in a "higher and more prolonged plasma probenecid concentration". Sawchuk Decl. at ¶ 46. Due to the overall characteristics associated with subcutaneous administration, *Guerrini* reports that such a mode of administration is preferred over intramuscular administration under the conditions of its study. *Id.* at 46. Dr. Sawchuk concludes that "*this is an example where subcutaneous administration achieves a certain desired result but where intramuscular administration does not accomplish the same result*." *Id.* (italics added).

In contrast to the pharmacokinetic profiles observed in *Guerrini*, in another study, subcutaneous administration of clindamycin, an antibiotic, resulted in faster absorption compared to intramuscular injection. Lavy E, Ziv G, Shem-Tov M, Glickman A, Dey A.,

"Pharmacokinetics of clindamycin HCl administered intravenously, intramuscularly and subcutaneously to dogs", *J Vet Pharmacol Ther.* 22(4):261-5 (1999) ("*Lavy*"); Sawchuk Decl. at ¶ 47. Nevertheless, the pharmacokinetic profiles in *Lavy* were such that subcutaneous administration maintained a therapeutic plasma concentration for a longer period of time than intramuscular administration. Sawchuk Decl. at ¶ 49. Based on the results from *Lavy*, Dr. Sawchuk concludes that in that case, "*one of ordinary skill in the art would not have been able to rely on data from subcutaneous administration to predict results of intramuscular administration because intramuscular administration would not have produced the same level of long-term efficacy achieved by subcutaneous administration*." *Id.* (italics added).

In yet another study highlighting the lack of correlation between subcutaneous and intramuscular administration, Dr. Sawchuk gives an example where, in contrast to the results from *Lavy*, the absorption of the drug was more rapid and complete following intramuscular dosing than after subcutaneous injection. Ismail M., "Disposition kinetics of difloxacin after intravenous, intramuscular and subcutaneous administration in calves", *Vet Res Commun*., 31(4):467-76 (2007) ("*Ismail*"); Sawchuk Decl. at ¶ 50. Dr. Sawchuk states that for the purposes in *Ismail*, the intramuscular administration was preferred to subcutaneous administration. Sawchuk Decl. at ¶ 52. Dr. Sawchuk explains that "[i]n this case, contrary to the two examples above, the intramuscular administration was considered to be associated with greater clinical efficacy." *Id.*

Dr. Sawchuk summarizes that "[t]hese three examples above show that there are significant differences in the rate and extent of absorption of a drug given by the intramuscular and subcutaneous route, even when given to the same animals in a

crossover study." *Id.* at ¶ 53. Dr. Sawchuk concludes that "[a]s a result, it cannot be predicted a priori whether intramuscular or subcutaneous dosing will result in more rapid and/or complete drug absorption, as examples of both cases are found in the scientific literature." *Id.* Dr. Sawchuk further explains that the examples above "*underscore the fact that efficacy of a given drug administered by a given route of dosing (e.g., intramuscular) cannot be known until appropriate comparative studies are performed in a suitable animal model.*" *Id.* at ¶ 54 (emphasis added). Dr. Sawchuk indicates that "[f]or some drugs, the desired effect might be achieved following a particular route of dosing, but for other drugs it might not," which underlies the lack of expectation that results from subcutaneous administration could be indicative of results obtained from intramuscular administration. *Id.*

With respect to the specific results from *McLeskey*, Dr. Sawchuk concludes that "one of ordinary skill in the art having the very limited experimental subcutaneous data from *McLeskey* would not have had an expectation that the intramuscular administration of fulvestrant using the *McLeskey* castor oil composition would have been effective following intramuscular administration, such as in the method described in the claims." *Id.* at ¶ 55.

For at least this additional reason, the instant claims are not obvious in light of the cited references and Applicants respectfully request that this rejection be withdrawn.

b) ***Independent Reason 4.*** **Numerous variables affect the efficacy of an intramuscular formulation (e.g.,. identity and proportion of cosolvents) and a POSITA would have understood that the resulting variability precludes a POSITA from having an expectation a priori that a given formulation would be successful in a given method of treatment until actual suitable in vivo experiments are performed**

Dr. Sawchuk explains that "[t]ypically, during the development of an intramuscular dosage form for administration of a drug in humans, one would have carried out, among other tasks, formulation studies to determine suitable compositions in which the drug of interest is dissolved, as well as initial intramuscular dosing experiments in animals (e.g., mice, rabbits, and/or dogs) under various conditions (e.g., different compositions, different solvents, varying the proportion of the components of the composition, different drug concentrations, etc.) in order to gain an understanding of the pharmacokinetics of fulvestrant before attempting human administration." Sawchuk Decl. at ¶ 58

Dr. Sawchuk highlights that by its very nature, the "existence of this generalized approach highlights the lack of expectation of success with respect to the extrapolation of the *McLeskey* disclosure of subcutaneous administration to mice, lacking any pharmacokinetic information, to human intramuscular administration." *Id.*

With respect to formulation studies, Dr. Sawchuk cites to the Gellert Declaration as disclosing the importance of performing additional formulation studies in order to attempt to minimize potential side effects arising from the presence of co-solvents. *Id.* at ¶ 59-61.

Dr. Sawchuk explains, however, that "[r]egardless of how high or low the cosolvent concentrations are in a given formulation, the preparation of formulations in which a drug such as fulvestrant can be solubilized is not sufficient to ensure the desired therapeutic effect when such formulation is administered in vivo." *Id.* at ¶ 62. Dr. Sawchuk cites to the instant specification as warning that "[s]imply solubilising fulvestrant in an oil based liquid formulation is not predictive of a good release profile or lack of precipitation of drug after injection at the injection site." *Id.* (citing the specification at ¶ [0054]). Thus, Dr. Sawchuk concludes that "suitable experiments are needed to determine the pharmacokinetic performance of any candidate formulation(s)." *Id.*

According to Dr. Sawchuk, as part of that process to develop methods of human treatment, and in order to discriminate among the various formulations in development, "pharmacokinetic data could be used to characterize important variables" in the process of developing a suitable method of treatment. In the case of "drugs that are difficult to formulate, such as fulvestrant, the pharmacokinetic data could be useful to investigate the most promising formulation for the desired route of administration." *Id.* at ¶ 63 (internal quotations omitted).

Dr. Sawchuk indicates that in a study testing seven different 100 mg/ml fulvestrant formulations intramuscularly in rabbits, the resulting pharmacokinetic data showed variability dependent on the proportion of the components in the formulations. *Id.* at ¶ 64 (citing data in PCT Application Publication No. WO 03/006064 ("WO 03/006064")). All of the fulvestrant formulations tested contained ethanol, benzyl alcohol, and benzyl benzoate in a castor oil vehicle, which are the same components of

the fulvestrant composition recited in the claims, but with different proportions for each component. *Id.*

Dr. Sawchuk explains that according to WO 03/006064, "[p]lasma levels were more variable than Control over the first 30 days following intramuscular administration of fulvestrant." *Id.* at ¶ 65 (internal quotations omitted). Based on differences observed in the pharmacokinetic profiles, the formulations were divided into two groups, Group A, which "demonstrates "rapid release early time points, corresponding to formulations containing lower benzyl benzoate and low castor oil concentrations, while Group B shows a lower release, flatter profile corresponding to formulations containing lower benzyl benzoate and higher castor oil concentrations." *Id.* (internal quotations omitted).

Summarizing the results in WO 03/006064, Dr. Sawchuk states that "higher benzyl benzoate concentrations in the formulation resulted in a more rapid initial release of fulvestrant, whereas lower benzyl benzoate concentrations resulted in a lower initial release, and a flatter plasma level profile." *Id.* at ¶ 66. Dr. Sawchuk concludes that "[d]epending on the overall objective of the administration of fulvestrant, some of the fulvestrant formulations tested in WO 03/006064's study would be more desirable than others for that given purpose and, based on the relevant pharmacokinetic profiles, one of ordinary skill in the art would be able to select one of those fulvestrant formulations for further development and/or testing." *Id.*

Nonetheless, Dr. Sawchuk explains that "one of ordinary skill in the art would not have been able to determine whether a given fulvestrant formulation injected intramuscularly as in WO 03/006064 would have had the desired pharmacokinetic profile until such in vivo pharmacokinetic studies were carried out." *Id.* at ¶ 67

Based on the differences in pharmacokinetic profiles from WO 03/006064, Dr. Sawchuk reiterates that "one of ordinary skill in the art knowing only the composition of a given formulation administered subcutaneously, but having no pharmacokinetic data from its intramuscular administration, would have had no expectation, one way or another, that the formulation would be effective when administered intramuscularly in a given method of treatment." *Id.* at ¶ 68.

In particular, with respect to the disclosure in *McLeskey*, Dr. Sawchuk indicates that "one of ordinary skill in the art would not have had a reasonable expectation that the *McLeskey* castor oil composition would have been effective when given as an intramuscular injection, such as in the method of treatment recited in the claims" *Id.* at ¶ 69.

Thus, for this additional independent reason, the instant claims are not obvious over the references cited and Applicants respectfully request that this rejection be withdrawn.

VI. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not included with this Response to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 17, 2012

By:_____

Carlos M. Téllez
Reg. No. 48,638
(202) 408-4123

PATENT
Attorney Docket No. 11285.0056-00000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
John R. Evans et al.	)	Group Art Unit: 1628
	)	
Application No.: 12/285,887	)	Examiner: HUI, San Ming R.
	)	
Filed: October 15, 2008	)	Confirmation No.: 1199
	)	
For: FORMULATION	)	**VIA EFS-WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132 OF RONALD J. SAWCHUK

I, **Ronald J. Sawchuk**, declare as follows:

Qualifications

1. My academic background and work experience are summarized in my curriculum vitae, which is attached as **Exhibit 1**.

2. Currently, I am a Professor of Pharmaceutics, Emeritus, and Morse Alumni Distinguished Teaching Professor. I am also the Director of the Bioanalytic and Pharmacokinetic Services Laboratory at the University of Minnesota.

3. I obtained a Bachelor of Science Degree in Pharmacy in 1963 from the University of Toronto. I also received a Masters of Science Degree in Pharmaceutics from the University of Toronto in 1966 and completed a Doctoral Degree (Ph. D.) in Pharmaceutical Chemistry (pharmacokinetics emphasis) at the University of California, San Francisco in 1972.

4. I joined the University of Minnesota in 1971 as an Instructor in Pharmaceutics, and served from 1972 to 1977 as an Assistant Professor of Pharmaceutics, from 1977 to 1983 as an Associate Professor of Pharmaceutics, and as a full Professor of Pharmaceutics from 1983 until my retirement in July of 2010.

5. At the University of Minnesota, I served as a member of the graduate programs in Pharmaceutics, Neurosciences, and Experimental and Clinical Pharmacology. From 1983 to 1989 and 1991 to 1994 I was the Director of Graduate Studies in Pharmaceutics at the University. From 1998 to 1999 I served as the Head of the Department of Pharmaceutics at the University of Minnesota.

6. Also, from 1982 to 1995, I served as Director of the Clinical Pharmacokinetics Laboratory at the College of Pharmacy at the University of Minnesota.

7. During my career, I received several honors, scholarships and awards, including the Weaver Medal of Honor in 2001, the Meritorious Manuscript Award from the American Association of Pharmaceutical Scientists in 1999 and the Hallie Bruce Memorial Lecture Award in 1996. In 2007, I received the American Pharmacists Association (APhA) Research Achievement Award in the Basic Pharmaceutical Sciences.

8. I am a member of numerous scientific and clinical societies. I am a Fellow of the American Association of Pharmaceutical Scientists and of the American Association for the Advancement of Science. I have been a member of the International Society of Anti-infective Pharmacology and the International Society for the Study of

Xenobiotics (ISSX). I recently served as a member-at-large on the American Association of Pharmaceutical Scientists (AAPS) Executive Council.

9. I have served on the editorial boards of scientific journals such as the Journal of Pharmaceutical Sciences and the Saudi Pharmaceutical Journal. I am currently on the Editorial Board of the AAPS Journal, and on the ISSX Journal, Xenobiotica. I have also served on numerous advisory committees and review panels.

10. I have participated in multiple research projects focused in the areas of preclinical and clinical pharmacokinetics, both publicly and privately funded. I am a named author on over 100 refereed scientific publications, in addition to several book chapters, a book that I co-edited on drug bioavailability, and over 170 abstracts which have been presented at scientific meetings. I have also given hundreds of invited lectures.

11. I have significant experience in the areas of pharmaceutical research, pharmacokinetics, and drug development. Therefore, I believe that I am qualified to render the opinions set forth in this declaration.

12. I have read the Office Action dated September 16, 2011 ("Office Action"), which is attached as **Exhibit 2**. Among other rejections, I understand that the Office Action rejects the claims pending in the captioned application as unpatentable over the following references:

a. McLeskey et al., "Tamoxifen-resistant fibroblast growth factor-transfected MCF-7 cells are cross-resistant in vivo to the antiestrogen ICI 182,780 and

two aromatase inhibitors", *Clinical Cancel Research* 4:697-711 (1998) ("*McLeskey*", attached hereto as **Exhibit 3**);

b. European Patent Specification No. EP 0 346 014, which names Michael Dukes as inventor ("*Dukes*", attached hereto as **Exhibit 4**);

c. Osborne et al., "Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer", *J. National Cancer Institute*, 87(20):746-750 (1995) ("*Osborne*", attached hereto as **Exhibit 5**); and

d. the abstract of Wakeling et al., "ICI 182,780, a new antioestrogen with clinical potential", *J. Steroid Biochemistry & Molecular Biology*, 43(1-3):173-177 (1992) ("*Wakeling*", attached hereto as **Exhibit 6**);

13. I have read the instant application ("the '887 application"), which I believe corresponds to U.S. Application Publication No. US 2010/0152149 (attached hereto as **Exhibit 7**.)

14. I attach hereto **Exhibit 8**, which I believe is a copy of the pending claims in the '887 application with proposed amendments. I understand the claims in **Exhibit 8** will be filed in the Patent and Trademark Office as part of the response to the Office Action.

15. I understand that the earliest priority date for the '887 application is January 10, 2000. In the paragraphs below, I will refer to the state of the art in the areas of pharmaceutical research, pharmacokinetics, and drug development prior to January 10, 2000. I will also explain how a person of ordinary skill in that art at that time

would have understood the references cited in the Office Action and how such a person would have interpreted certain experimental results related to various fulvestrant formulations.

Disclosure in *McLeskey* regarding the castor oil fulvestrant composition

16. *McLeskey* discloses two fulvestrant compositions. One composition was prepared by dissolving powdered drug in 100% ethanol and then spiking it into warmed peanut oil to give a final concentration of 50 mg/ml ("the *McLeskey* peanut oil composition"). *McLeskey* at 698, col. 2, under "Drugs". The second composition is a 50 mg/ml fulvestrant composition "in a vehicle of 10% ethanol, 15% benzyl benzoate, 10% benzyl alcohol, brought to volume with castor oil" ("the *McLeskey* castor oil composition"). *Id*. *McLeskey* does not specify whether the percentages in the castor oil composition are in weight/volume units (% w/v, as recited in the claims of the '887 application) or in volume/volume units (% v/v).

17. In a liquid composition, when a solute or cosolvent is a liquid, it is often convenient to express its concentration as a volume percent, i.e., % v/v. For the reasons that follow, I believe one of ordinary skill in the art would have concluded the *McLeskey* castor oil composition was described in volume/volume units (% v/v).

18. For example, U.S. Patent No. 3,164,520 ("the '520 patent", attached as **Exhibit 9**) entitled "Injectable Steroid Compositions Containing at least 75% Benzyl Benzoate" discloses the preparation of parenteral injections of steroid drugs in formulations containing benzyl benzoate, and often also containing castor oil or sesame oil. *See*, *e.g.*, the working examples. The '520 patent states: "The amount of benzyl

benzoate which may be employed in the compositions of this invention while still yielding satisfactory results has been found to range from about 75% to 100% by volume of the pharmaceutical vehicle employed." The '520 patent at col. 2, ll. 10-14. In addition, each of the four claims of the '520 patent refers to a parenteral steroid formulation in a pharmaceutical vehicle or pharmaceutical carrier wherein at least 75% by volume of said vehicle is benzyl benzoate.

19. Raymond Huber, the named inventor of the '520 patent, is a co-author of a similar publication in which parenteral formulations of steroid hormones in castor oil are described. Riffkin, C., Huber, R., and Keysser, C.H., "Castor oil as a vehicle for parenteral administration of steroid hormones", *J Pharm Sci*, 53(8): 891-95 (1964) ("*Riffkin*", attached as **Exhibit 10**). *Riffkin* lists the compositions of various vehicles prepared in Tables IV to VI, which reference liquid components and their proportions in the overall composition in terms of percentage units ("%"). Although *Riffkin* does not specifically state that those compositions are % v/v, one would understand them to be % v/v because *Riffkin* refers to the concentrations of the solid solutes (the steroids) in terms of w/v, (e.g., mg./ml.), whereas the concentrations of the liquid components are simply reported in terms of "%" units. *See*, *e.g.*, Tables V and VI. One would reasonably assume that, had *Riffkin* intended the concentration of the liquid components to be in terms of % w/v units, *Riffkin* would have explicitly indicated that fact, as it did for the solid components. Footnote 4 is another example of the use of the above nomenclature. Footnote 4 refers to the concentration of estradiol valerate in the injectable formulations, in terms of "mg./ml.", but refers to a "%" value for the liquids—

castor oil, benzyl benzoate, and benzyl alcohol. Therefore, one would conclude that the composition of the solvents in *Riffkin's* vehicles is expressed as % v/v.

20. Other publications also describe the composition of injectable formulations comprising liquid solvents or co-solvents on a "by volume" basis. For example, a published review tabulates various excipients included in the formulation of injectable products marketed in the Unites States. Neema, S, Washkuhn, R.J., and Brendel, R.J., "Excipients and their use in injectable products", *PDA J Pharm Sci Tech*, 51(4):166-171 (1997)("*Neema*", attached as **Exhibit 11**). *Neema* lists liquid solvents, co-solvents, and solubilizing agents, and identifies commercial products in which the content of such liquid agents is described on a % v/v basis (e.g., benzyl benzoate, 20% v/v; PEG 40 castor oil, 11.5% v/v; sorbitol, 50% v/v). *See*, *e.g.*, Tables I and II.

21. Considering the above examples, and because all of the components of the vehicle disclosed in *McLeskey* are liquids, one of ordinary skill in the art would have concluded that the composition was described in terms of volume/volume percent units (% v/v).

22. Therefore, one of ordinary skill in the art would have concluded that the *McLeskey* castor oil composition on page 698 was reported in % v/v units and referred to a composition containing 10% **v**/v ethanol, 15% **v**/v benzyl benzoate, and 10% **v**/v benzyl alcohol in a castor oil vehicle. This composition *is different* from a composition containing 10% **w**/v ethanol, 15% **w**/v benzyl benzoate, and 10% **w**/v benzyl alcohol in a castor oil vehicle.

23. It is possible to convert % v/v values for a given component in a liquid composition into % w/v values by calculating the weight of the corresponding volume of that component in the composition. As a first approximation, the weight of the component can be calculated by multiplying the volume of the component by its density.

24. In order to facilitate this calculation, I assumed the preparation of 100 ml of the *McLeskey* castor oil composition and reported the associated volume and weight values in Table 1 below, using densities reported or calculated at 25°C. The resulting % w/v values are independent of the choice of a particular volume of the *McLeskey* castor oil composition for this calculation. However, a volume of 100 ml of the castor oil composition was selected for simplicity to show the corresponding volumes and weights. The differences between % v/v and % w/v compositions for each of the three components can be seen by comparing the values in Columns A and E. It should be noted that although these compositions are identical, they are described differently; in Column A, the composition is described on a percentage "by volume" (% v/v) basis, and in Column E, the composition is described on a percentage "by weight" (% w/v) basis.

Table 1. Information for 100 ml of the fulvestrant *McLeskey* castor oil composition[1]

	A	B	C	D	E
Component	**% v/v**	**Volume (ml)**	**Density (mg/ml)**	**Weight (g)**	**% w/v**
Ethanol	10	10	0.808	8.08	8.1
Benzyl Benzoate	15	15	1.118	16.77	16.8
Benzyl Alcohol	10	10	1.04156	10.42	10.4

25. In Table 1, Column A represents the concentration of each component in the *McLeskey* castor oil composition in % **v**/v units (i.e., as one of ordinary skill in the art in would have understood the *McLeskey* disclosure). Column B represents the volume in milliliters (ml) of each component necessary to prepare 100 ml of the *McLeskey* castor oil composition.

26. Column C represents the density of each component in g/ml at 25ºC, reported or calculated from published relative density data from the Merck Index, **Exhibit 12**. The Merck Index reports specific gravity values for liquid substances as the ratio of the density of the substance at a given temperature relative to the density of water at a reference temperature. **Exhibit 12** at p. xiv (entry for "d"). Regarding the benzyl benzoate and benzyl alcohol values, their densities were reported at 25ºC and

[1] *McLeskey* does not indicate whether the ethanol used in its castor oil fulvestrant composition is dehydrated ethanol or the binary azeotropic ethanol composition containing about 96% ethanol by volume (see entry no. 3806 for ethanol in the Merck Index, 12th Ed., Merck & Co., Inc. (1996) at pp. 641-642 ("the Merck Index", relevant copies attached as **Exhibit 8**)). The value in Table 1 for the density of ethanol corresponds to the density of the azeotropic ethanol composition. The density of dehydrated ethanol is 0.789 mg/ml at 20ºC (**Exhibit 8**), which would produce an even lower w/v% value for ethanol than that reported in Table 1.

the density of water was reported at 4ºC (**Exhibit 12** at entries no. 1159, 1162; pp. 189-190). Because the density of water at 3.98ºC is 1.0000 g/ml (**Exhibit 12** at entry 10175; p. 1715), the values reported in the Merck Index for benzyl benzoate and benzyl alcohol were used in Table 1 as the corresponding densities in mg/ml (considering that 3.98ºC is 4ºC for purposes of this calculation). For ethanol, the Merck Index reports a specific gravity of 0.810 at 25ºC with respect to the density of water at 25ºC (**Exhibit 12** at entry no. 3806; p. 642). Thus, to obtain the density of ethanol (the binary azeotrope) at 25ºC, I multiplied the density of water at 25ºC, 0.997 mg/ml (**Exhibit 12** at entry no. 10175; p. 1715), by the specific gravity reported in the Merck Index (0.810) to produce a value of 0.808 mg/ml for the density of ethanol at 25ºC.

27. Column D represents the weight of each component, obtained by multiplying the volume of each component (Column B) by its density (Column C). Column E represents the concentration of each component in the *McLeskey* castor oil composition in w/v% units, which is the weight of each component (Column D) in 100 ml of solution (the total volume of the composition) after rounding the value to a single decimal place.

28. Accordingly, based on the values in Table 1, a composition containing 10% v/v ethanol, 15% v/v benzyl benzoate, and 10% v/v benzyl alcohol translates into a composition containing about 8.1% w/v ethanol, about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol.

29. Thus, one of ordinary skill in the art reading *McLeskey* would have concluded that *McLeskey* described a composition containing about 8.1% w/v ethanol,

about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol in a castor oil vehicle.

30. Neither *McLeskey* nor any of the references cited in the Office Action contain any disclosure that would have suggested to one of ordinary skill in the art the modification of a composition containing about 8.1% w/v ethanol, about 16.8 % w/v benzyl benzoate, and about 10.4% w/v benzyl alcohol (i.e., the *McLeskey* castor oil composition) in an attempt to produce a composition as recited in the claims containing about 10% w/v ethanol, about 15% w/v benzyl benzoate, and about 10% w/v benzyl alcohol.

Disclosure in *McLeskey* regarding administration of fulvestrant compositions

31. As mentioned above, *McLeskey* disclosed two different fulvestrant compositions, the peanut oil composition and the castor oil composition. *McLeskey* at 698. *McLeskey*, however, did not provide any experimental data that would have allowed one of ordinary skill in the art to compare any aspect of the performance of the two fulvestrant compositions for the treatment of cancerous tumors. Therefore, *McLeskey* provided no information that would have suggested to one of ordinary skill in the art the desirability of either of its fulvestrant compositions over other known fulvestrant formulations.

32. *McLeskey* did not disclose plasma or blood levels of fulvestrant in mice after subcutaneous administration of either the peanut oil or the castor oil compositions. Thus, no information regarding the rate and/or extent of absorption of fulvestrant from

the subcutaneous injection site is available to one of ordinary skill in the art for either composition.

33. *McLeskey* concluded that treatment with fulvestrant (ICI 182,780), using either of the disclosed compositions was not effective in that it "did not slow estrogen-independent growth or prevent metastasis of tumors produced by FGF-transfected MCF-7 cells in ovariectomized nude mice." *McLeskey* at Abstract. Thus, one of ordinary skill in the art would not have been informed about the usefulness of either fulvestrant formulation when administered subcutaneously to a mouse for the treatment of cancerous tumors.

34. *McLeskey* also reports that fulvestrant "retained activity" based on the results from injecting fulvestrant into "reproductively intact female mice for two weeks . . . at the same doses used in the above experiment" and the uteri subsequently harvested from those mice "weighed less than those from control mice and exhibited a complete lack of endometrial glandular structures (data not shown)." *Id.* at ¶ bridging 701-702. Unfortunately, *McLeskey* does not specify which of the two fulvestrant formulations, if any, (the peanut oil composition or the castor oil composition), was used in these experiments. *McLeskey* does not disclose the route of administration (subcutaneous, intramuscular, intraperitoneal, etc.) for the injection of fulvestrant into those "reproductively intact female mice." Thus, one of ordinary skill in the art reading *McLeskey* cannot draw any conclusions regarding the extent to which fulvestrant administered subcutaneously became absorbed, if at all, when using the peanut oil or the castor oil compositions.

35. Indeed, because of the lack of fulvestrant efficacy and the absence of pharmacokinetic data in *McLeskey*, one of ordinary skill in the art would have been unable to conclude whether either of the two fulvestrant *McLeskey* compositions (peanut oil or castor oil) was able to deliver a dose of fulvestrant that had an antitumor therapeutic effect in the mice when administered subcutaneously, nor any insight about fulvestrant absorption characteristics (rate and extent) when administered via the *intramuscular route* in any species, including humans.

36. Thus, *McLeskey* provides no information that would have led one of ordinary skill in the art to have a preference for either the peanut oil or the castor oil fulvestrant compositions over the other one, or even a preference for one of the two *McLeskey* fulvestrant compositions over other fulvestrant compositions known in the art prior to January 10, 2000.

37. While I have not performed a search for fulvestrant compositions known in the art prior to January 10, 2000, I note that some of the references cited by the Examiner in the Office Action do disclose other fulvestrant compositions. For example, *Osborne* discloses experiments in which a composition of fulvestrant "in castor oil" was injected subcutaneously to female nude mice. *Osborne* (**Exhibit 5**) at 747, col. 1. Based on the positive results of those experiments, *Osborne* concludes that fulvestrant "is a more effective estrogen antagonist than tamoxifen in the MCF-7 tumor cell/nude mouse model system." *Osborne* at Abstract.

38. The fulvestrant composition in *Wakeling* is described as having fulvestrant "in oil suspension" for parenteral administration to mice. *Wakeling* (**Exhibit 6**) at

Abstract. *Wakeling* reports that, "over a 1 month period, a single injection of [fulvestrant] in oil suspension achieved effects comparable with those of daily tamoxifen treatment." *Id.*

39. *Dukes* discloses two different fulvestrant compositions for intramuscular injection, one containing fulvestrant dissolved "in a mixture of propylene glycol: ethanol: water: poloxamer 407" administered daily by intramuscular injection to rats. *Dukes* (**Exhibit 4**) at Example 2, p. 8. The second composition contained 50 mg of fulvestrant, "400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml." *Id.* at Example 3, p. 9. For each composition, *Dukes* reports that "at all doses tested the compound [fulvestrant] selectively inhibits the action of the animals' endogenous oestrogen on their uteri." *Id.* at Examples 2 & 3, pp. 8-9.

40. Thus, it is clear that one of ordinary skill in the art had other choices besides the *McLeskey* castor oil composition with respect to potential fulvestrant formulations that could have been further investigated for the development of a method of treating humans with intramuscular fulvestrant. However, none of the references cited in the Office Action provides any information that would have guided one of ordinary skill in the art to select the *McLeskey* castor oil composition, over any of the other fulvestrant compositions mentioned above, for the potential development of such a method of treatment.

41. Moreover, none of the references cited by the Examiner provides any guidance as to the relevant factors to consider when selecting a formulation for the potential development of a method of treatment as recited in the instant claims.

However, judging solely on the basis of efficacy, the *McLeskey* castor oil composition would have been among the least favored compositions to select for further development from the fulvestrant compositions discussed above because the *McLeskey* experiments were ineffective and one of ordinary skill in the art would not have been able to conclude from the information in *McLeskey* whether fulvestrant, using that composition, was sufficiently bioavailable to have an antitumor effect. In this regard, and considering only efficacy, the fulvestrant oil suspension from *Wakeling* would have been among the most favored formulations to select for further development from among those discussed above because at least that formulation, when given as a single injection, showed a therapeutic antitumor effect in mice for over a one-month period.

Lack of disclosure in *McLeskey* regarding intramuscular efficacy of either fulvestrant composition disclosed therein

42. The mode of administration of a drug (e.g., oral, intramuscular, subcutaneous, etc.) and the dose administered affects the release profile of the drug. One of ordinary skill in the art would have understood that results from subcutaneous administration in general, and including those reported in *McLeskey*, cannot be extrapolated to intramuscular administration. As a result, one of ordinary skill in the art would not have had an expectation as to whether the *McLeskey* castor oil composition would have had a therapeutic effect when administered intramuscularly before actually performing suitable *in vivo* experiments.

43. There is abundant evidence in the scientific literature that the intramuscular and subcutaneous administration of a drug to the same animal or human

may produce very different plasma level curves, and therefore very different pharmacologic effects. These effects include the desired effects (efficacy) and those that are not desired (adverse events, or side effects). If a drug is poorly absorbed from the injected site, (e.g., too slowly, or to only a modest extent) the drug may show no effects whatsoever.

44. For example, a study in sheep using probenecid, a drug which may be used to prolong the half-life of some antibiotics in animals, demonstrates significant differences in the absorption of intramuscular and subcutaneous injections of probenecid. Guerrini V.H., Filippich L.J., English P.B., Schneider J., Cao G.R. and Bourne D.W.A., "Pharmacokinetics of probenecid in sheep", *J Vet Pharmacol Ther.* 8(2):128-35 (1985) ("*Guerrini*", attached as **Exhibit 13**).

45. Those investigators administered probenecid to ewes in doses of 1 gram by both intramuscular and subcutaneous injection. *Guerrini* at 129. The study shows that the absorption of probenecid is more rapid and complete following intramuscular injection, compared to subcutaneous injection. *Id.* at Abstract. *Guerrini* reports that the bioavailability of the intramuscular dose was 135% of that of the subcutaneous dose (corresponding to an average bioavailability of 46% for intramuscular injection compared with an average bioavailability of 34% for subcutaneous injection). *Id.* The subcutaneous dose was also absorbed more slowly, with average plasma levels of the drug peaking at 1.5 hr, compared to 0.67 hr for the intramuscular dose. *Id*. at 131. Because of this slower absorption following subcutaneous dosing, probenecid plasma concentrations remained higher after 2 hours when the drug was administered

subcutaneously than when it was administered intramuscularly. *Id.* at 135. Consistent with these observations, the rate constant for absorption for the intramuscular dose was 41% greater than for the subcutaneous dose (5.45 vs. 3.87 hr^{-1}). *Id.* at 133.

46. In this case, despite the overall higher bioavailability of intramuscular probenecid, the "higher and more prolonged plasma probenecid concentration" following subcutaneous administration resulted in "similar plasma concentrations to those found in man after oral administration." *Id.* at 135. *Guerrini* concludes that "[t]he s.c. [subcutaneous] administration of probenecid in animals is preferred [to intramuscular administration] because muscle damage is avoided and it provided useful plasma concentrations." *Id.* Thus, this is an example where subcutaneous administration achieves a certain desired result but where intramuscular administration does not accomplish the same result.

47. Another study shows that, contrary to the pharmacokinetic profiles observed in *Guerrini*, subcutaneous administration resulted in faster absorption compared to intramuscular injection. Lavy E, Ziv G, Shem-Tov M, Glickman A, Dey A., "Pharmacokinetics of clindamycin HCl administered intravenously, intramuscularly and subcutaneously to dogs", *J Vet Pharmacol Ther.* 22(4):261-5 (1999) ("*Lavy*", attached as **Exhibit 14**).

48. *Lavy* reports that when a 10 mg/kg dose of clindamycin HCl, an antibioitic, was given subcutaneously to dogs, the average maximum blood serum concentration (Cmax) of clindamycin was 20.8 µg/ml, and the time when this maximum occurred (Tmax) averaged 46.7 min. *Lavy* at Table 3. When the same dose was given

intramuscularly to the same animals, the corresponding values for Cmax and Tmax were 4.4 µg/ml and 73 min, exhibiting a very much slower rate of absorption. *Id.* In addition, the exposure of the dogs to clindamycin, assessed through an analysis of the plasma serum area under the curve (AUC) was 2.9 times greater for the subcutaneous dose than for the intramuscular dose. *Id.* This means that the bioavailability of the subcutaneous dose of this drug is 2.9 times that of the intramuscular dose.

49. Based on the differences in pharmacokinetic profiles for subcutaneous and intramuscular administration, *Lavy* concludes that "it appears from the present study that the s.c. [subcutaneous] route is superior to the i.m. [intramuscular] in practical terms by permitting a longer treatment interval." *Id.* at 265. This is another example in which subcutaneous administration is able to fulfill certain design criteria (maintain a therapeutic plasma concentration for a longer period of time) better than intramuscular administration. Therefore, under these circumstances, one of ordinary skill in the art would not have been able to rely on data from subcutaneous administration to predict results of intramuscular administration because intramuscular administration would not have produced the same level of long-term efficacy achieved by subcutaneous administration.

50. There are other reports in the literature that show that, in contrast to the results from *Lavy*, the absorption of a drug is more rapid and complete following intramuscular dosing than after subcutaneous injection. For example, when the fluoroquinolone antimicrobial agent difloxacin was given by these routes to the same calves in a crossover study, the rates of absorption differed greatly, with intramuscular

injection showing higher and earlier peak plasma concentrations, confirming much more rapid absorption. Ismail M., "Disposition kinetics of difloxacin after intravenous, intramuscular and subcutaneous administration in calves", *Vet Res Commun.*, 31(4):467-76 (2007) ("*Ismail*", attached as **Exhibit 15**).

51. After intramuscular and subcutaneous dosing, maximum plasma concentrations (Cmax) of 3.38 and 2.18 µg/ml were observed after (Tmax) 1.22 and 3.7 hr, respectively. *Ismail* at Abstract. The time for half of the dose to be absorbed when given by intramuscular injection was only 0.38 hr, whereas the corresponding time for absorption of the subcutaneously injected dose was 2.1 hr, over 5 times as long. *Id.* at 473.

52. Under the conditions of its study, *Ismail* concludes that "the doses of difloxacin used in this study are likely to involve better pharmacodynamic characteristics that are associated with greater clinical efficacy following i.m. [intramuscular] administration than following s.c. [subcutaneous] administration." *Id.* at Abstract. In this case, contrary to the two examples above, the intramuscular administration was considered to be associated with greater clinical efficacy.

53. These three examples above show that there are significant differences in the rate and extent of absorption of a drug given by the intramuscular and subcutaneous route, even when given to the same animals in a crossover study. As a result, it cannot be predicted a priori whether intramuscular or subcutaneous dosing will result in more rapid and/or complete drug absorption, as examples of both cases are found in the scientific literature.